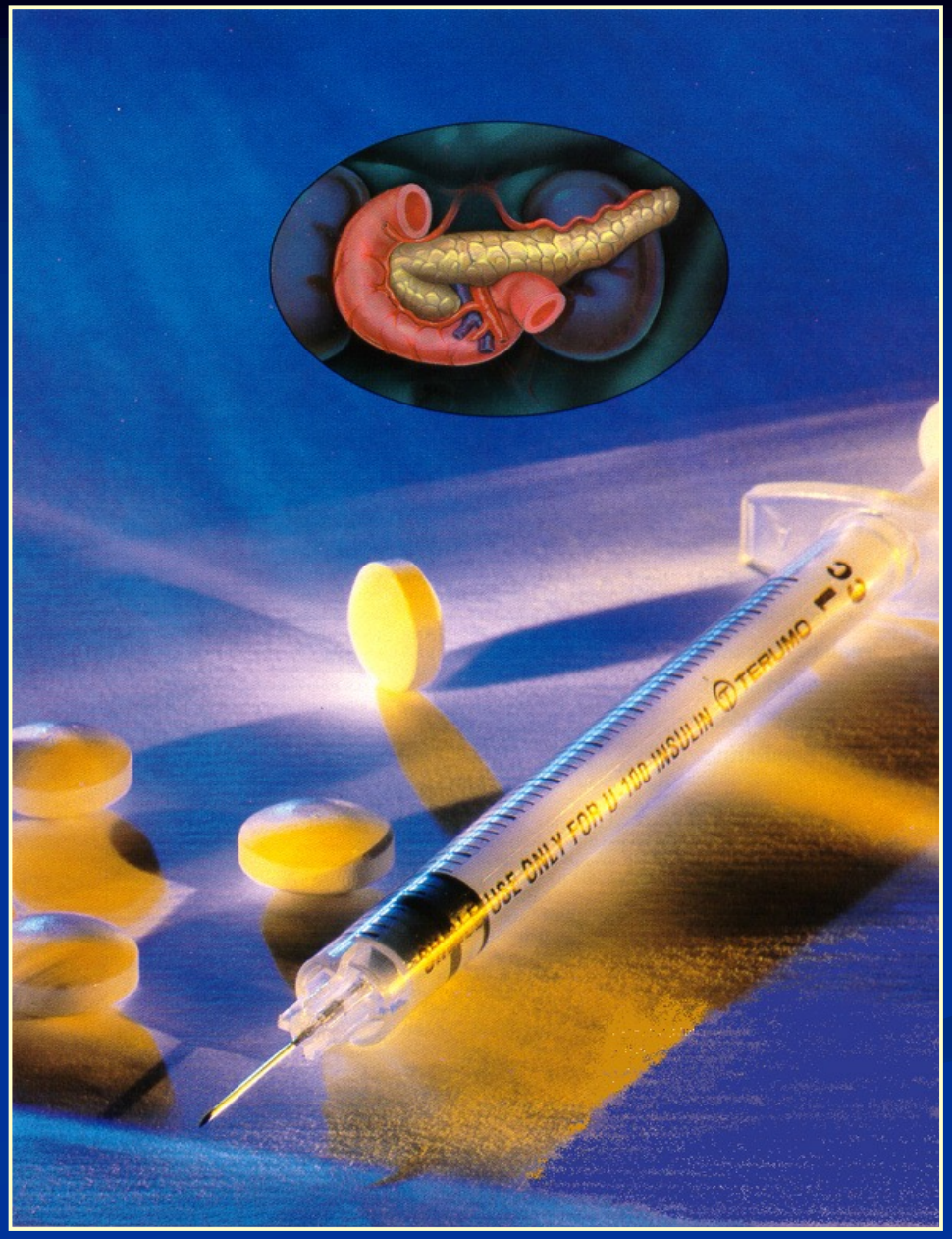
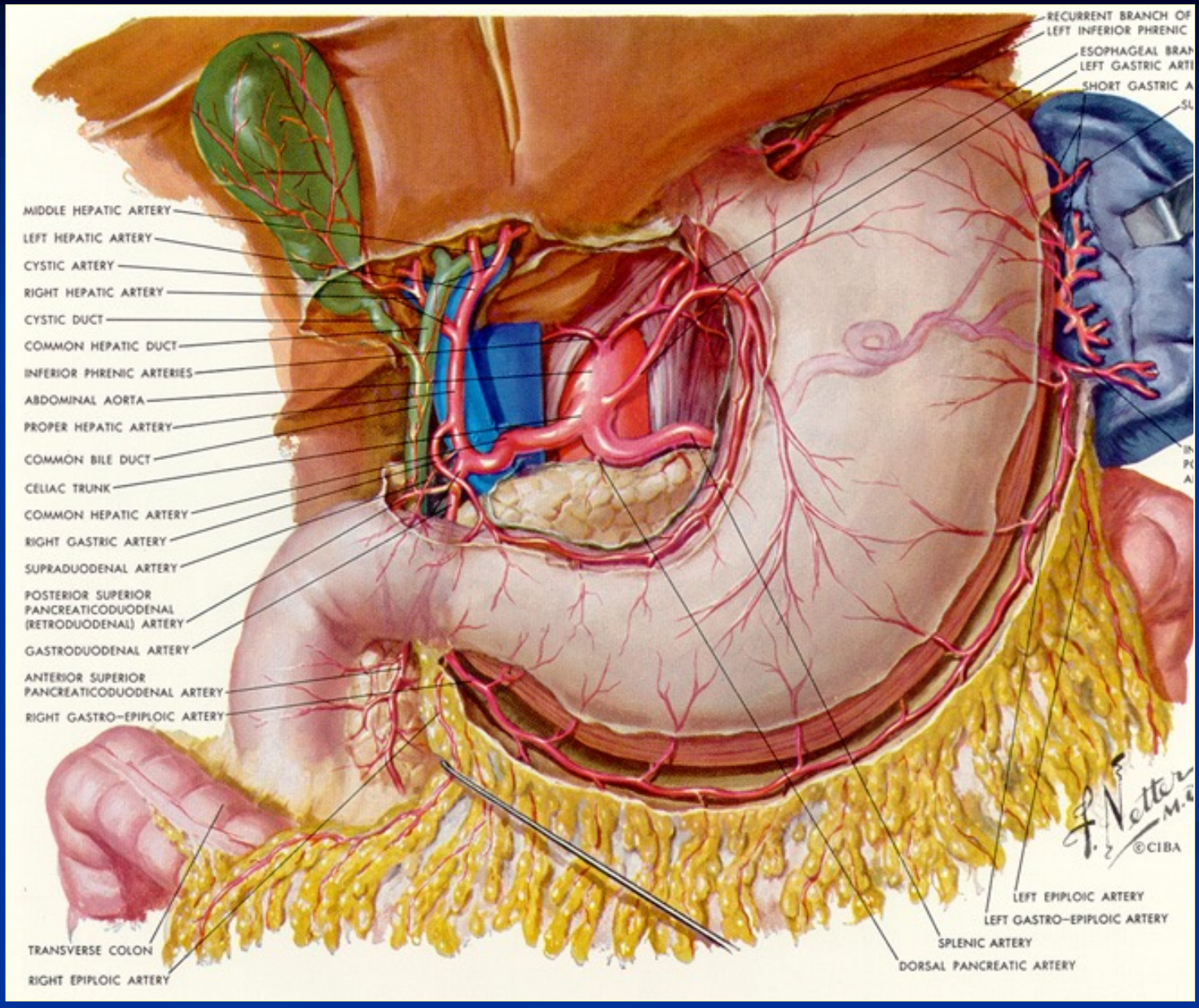
Pharmacologic Management of Diabetes Mellitus

Southern California University of Health Science



ANATOMY


RECURRENT BRANCH OF
LEFT INFERIOR PHRENIC
ESOPHAGEAL BRA
LEFT GASTRIC ARTE
SHORT GASTRIC A
MIDDLE HEPATIC ARTERY
LEFT HEPATIC ARTERY
CYSTIC ARTERY
RIGHT HEPATIC ARTERY
CYSTIC DUCT
COMMON HEPATIC DUCT
INFERIOR PHRENIC ARTERIES
ABDOMINAL AORTA
PROPER HEPATIC ARTERY
COMMON BILE DUCT
CELIAC TRUNK
COMMON HEPATIC ARTERY
RIGHT GASTRIC ARTERY
SUPRADUODENAL ARTERY
POSTERIOR SUPERIOR
PANCREATICODUODENAL
(RETRODUODENAL) ARTERY
GASTRODUODENAL ARTERY
ANTERIOR SUPERIOR
PANCREATICODUODENAL ARTERY
RIGHT GASTRO-EPIPLOIC ARTERY
TRANSVERSE COLON
RIGHT EPIPLOIC ARTERY
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LEFT GASTRO-EPIPLOIC ARTERY
SPLENIC ARTERY
DORSAL PANCREATIC ARTERY
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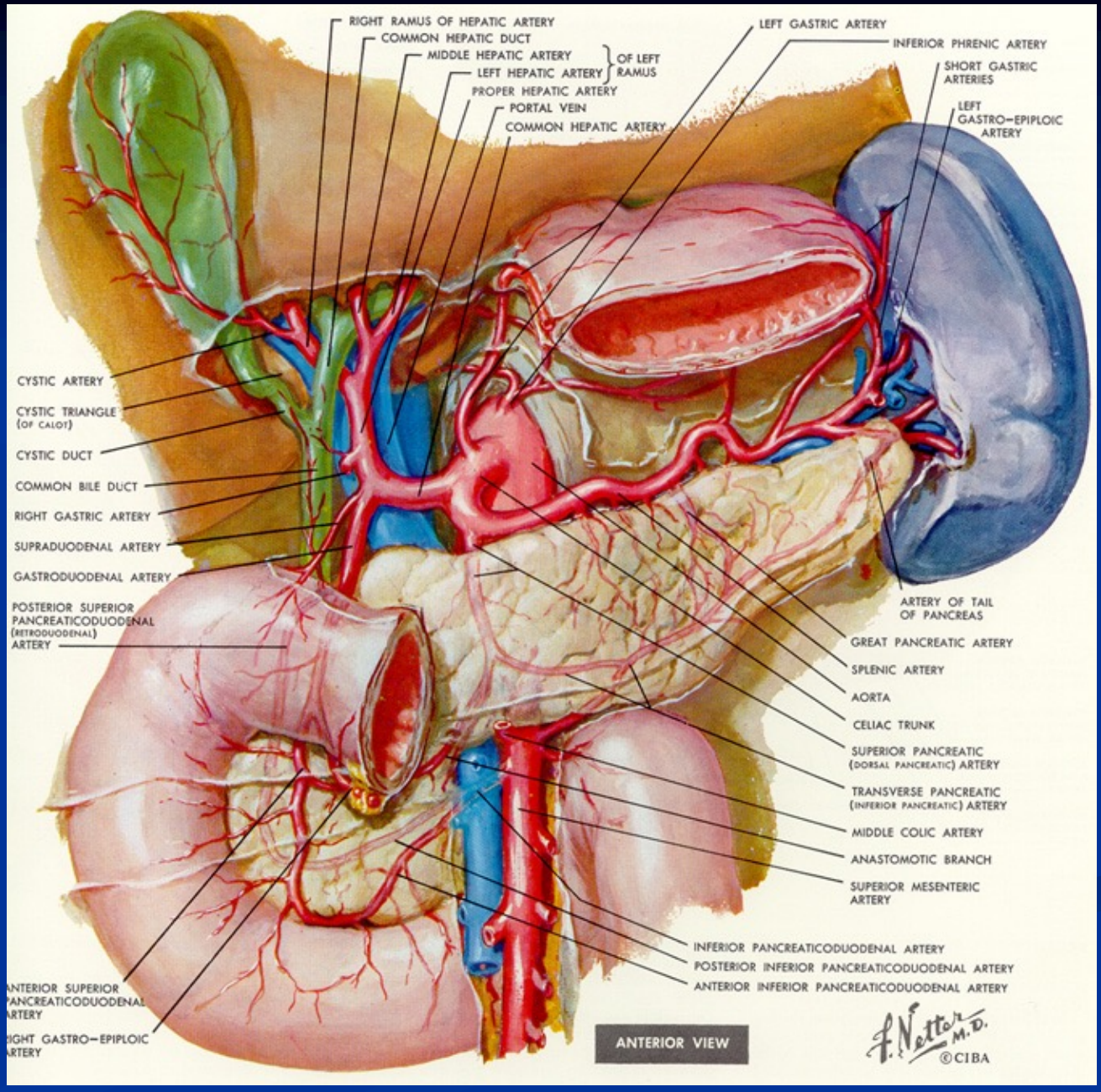
RIGHT RAMUS OF HEPATIC ARTERY
COMMON HEPATIC DUCT
MIDDLE HEPATIC ARTERY
LEFT HEPATIC ARTERY
OF LEFT RAMUS
PROPER HEPATIC ARTERY
PORTAL VEIN
COMMON HEPATIC ARTERY
LEFT GASTRIC ARTERY
INFERIOR PHRENIC ARTERY
SHORT GASTRIC ARTERIES
LEFT GASTRO-EPIPLOIC ARTERY
CYSTIC ARTERY
CYSTIC TRIANGLE (OF CALOT)
CYSTIC DUCT
COMMON BILE DUCT
RIGHT GASTRIC ARTERY
SUPRADUODENAL ARTERY
GASTRODUODENAL ARTERY
POSTERIOR SUPERIOR PANCREATICODUODENAL (RETRODUODENAL) ARTERY
ARTERY OF TAIL OF PANCREAS
GREAT PANCREATIC ARTERY
SPLENIC ARTERY
AORTA
CELIAC TRUNK
SUPERIOR PANCREATIC (DORSAL PANCREATIC) ARTERY
TRANSVERSE PANCREATIC (INFERIOR PANCREATIC) ARTERY
MIDDLE COLIC ARTERY
ANASTOMOTIC BRANCH
SUPERIOR MESENTERIC ARTERY
INFERIOR PANCREATICODUODENAL ARTERY
POSTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR SUPERIOR PANCREATICODUODENAL ARTERY
RIGHT GASTRO-EPIPLOIC ARTERY
ANTERIOR VIEW
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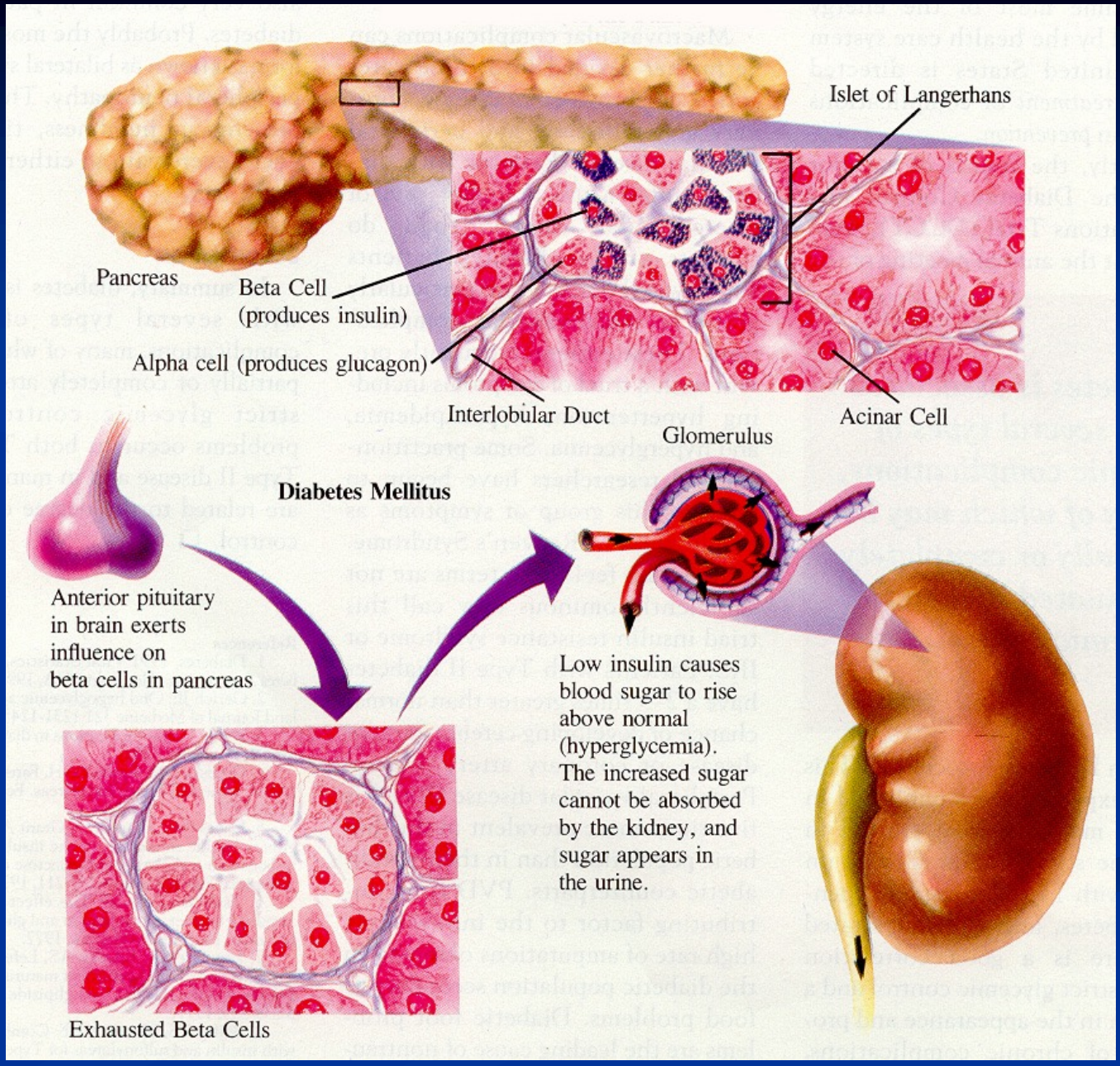
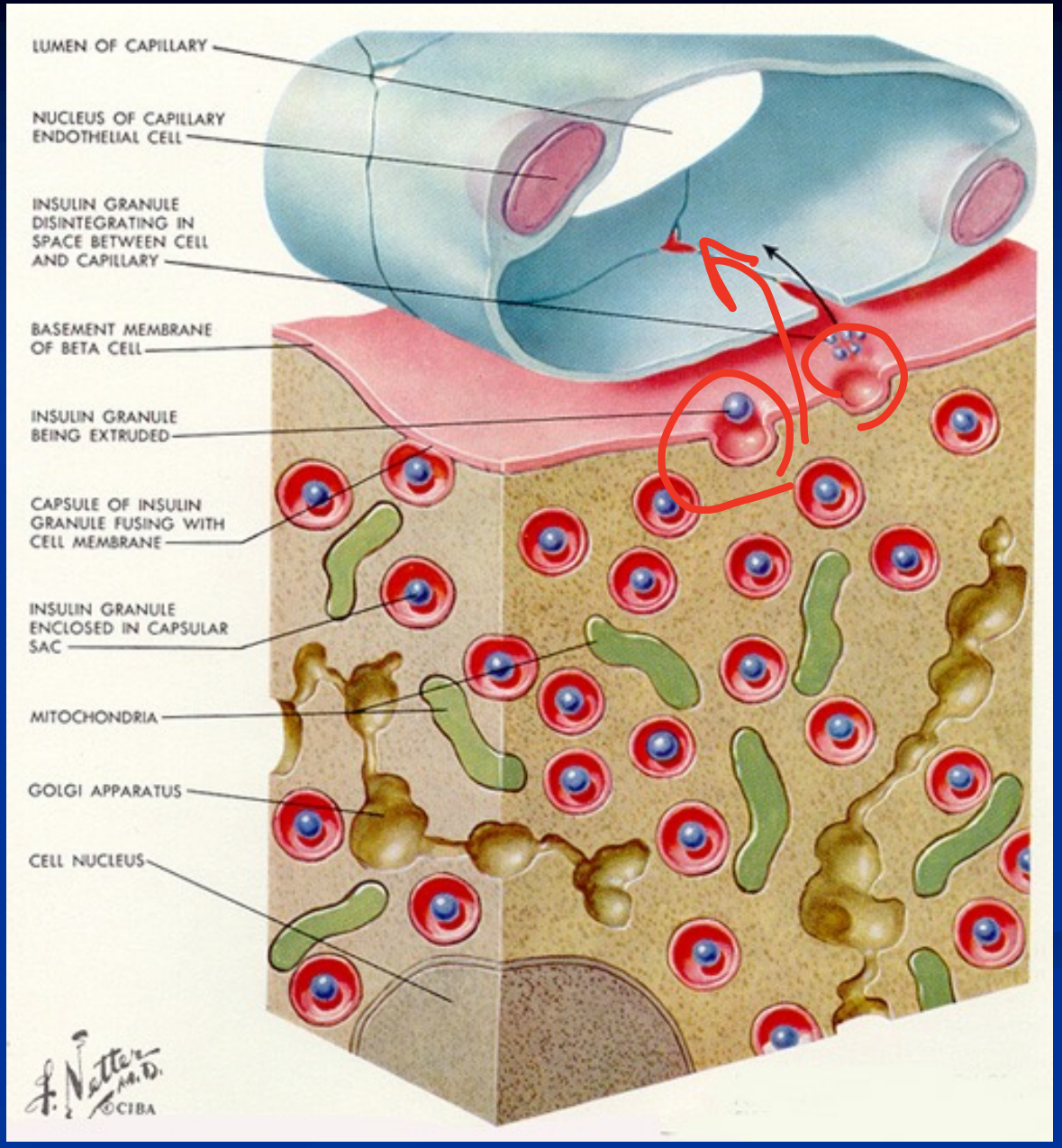
PHYSIOLOGY


Islet of Langerhans
Pancreas
Beta Cell
(produces insulin)
Alpha cell (produces glucagon)
Interlobular Duct
Acinar Cell
Glomerulus
Diabetes Mellitus
Anterior pituitary
in brain exerts
influence on
beta cells in pancreas
Low insulin causes
blood sugar to rise
above normal
(hyperglycemia).
The increased sugar
cannot be absorbed
by the kidney, and
sugar appears in
the urine.
Exhausted Beta Cells

PHYSIOLOGY


LUMEN OF CAPILLARY
NUCLEUS OF CAPILLARY ENDOTHELIAL CELL
INSULIN GRANULE DISINTEGRATING IN SPACE BETWEEN CELL AND CAPILLARY
BASEMENT MEMBRANE OF BETA CELL
INSULIN GRANULE BEING EXTRUDED
CAPSULE OF INSULIN GRANULE FUSING WITH CELL MEMBRANE
INSULIN GRANULE ENCLOSED IN CAPSULAR SAC
MITOCHONDRIA
GOLGI APPARATUS
CELL NUCLEUS
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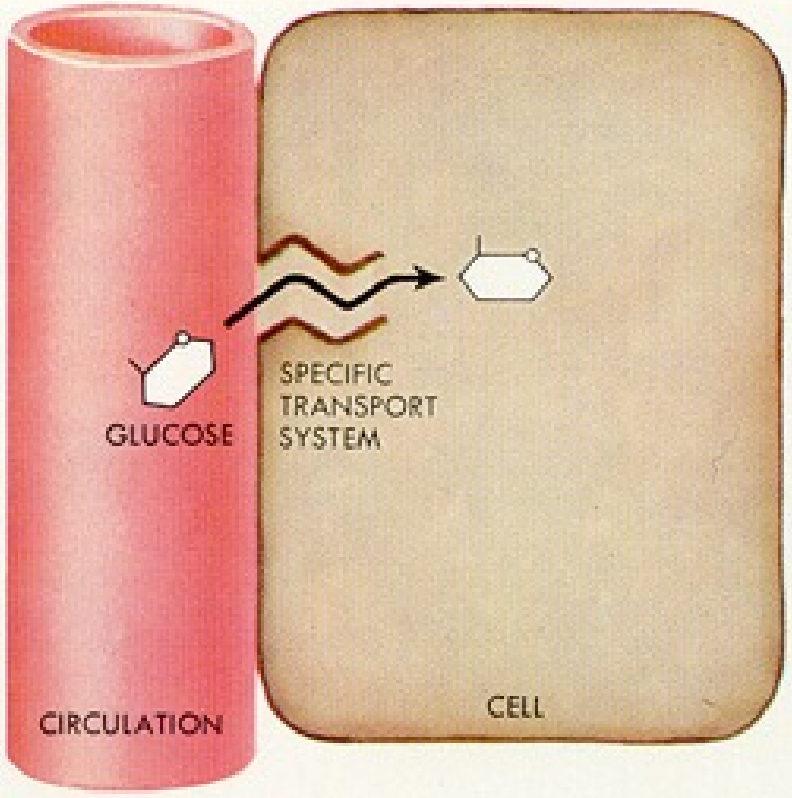
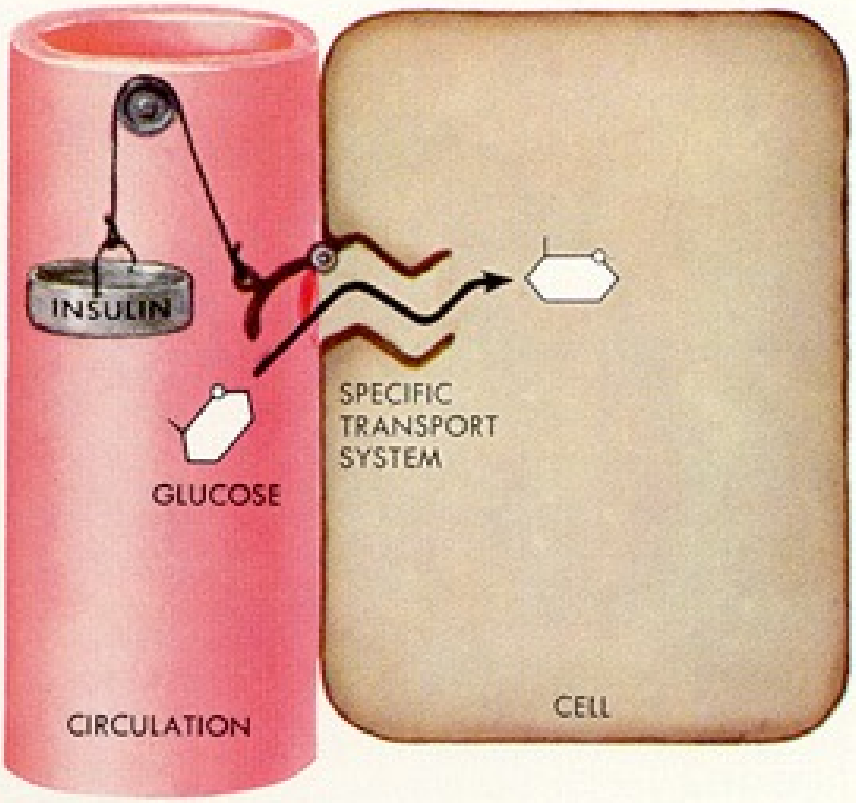
Function of Insulin



RED BLOOD CELLS; NEURONS

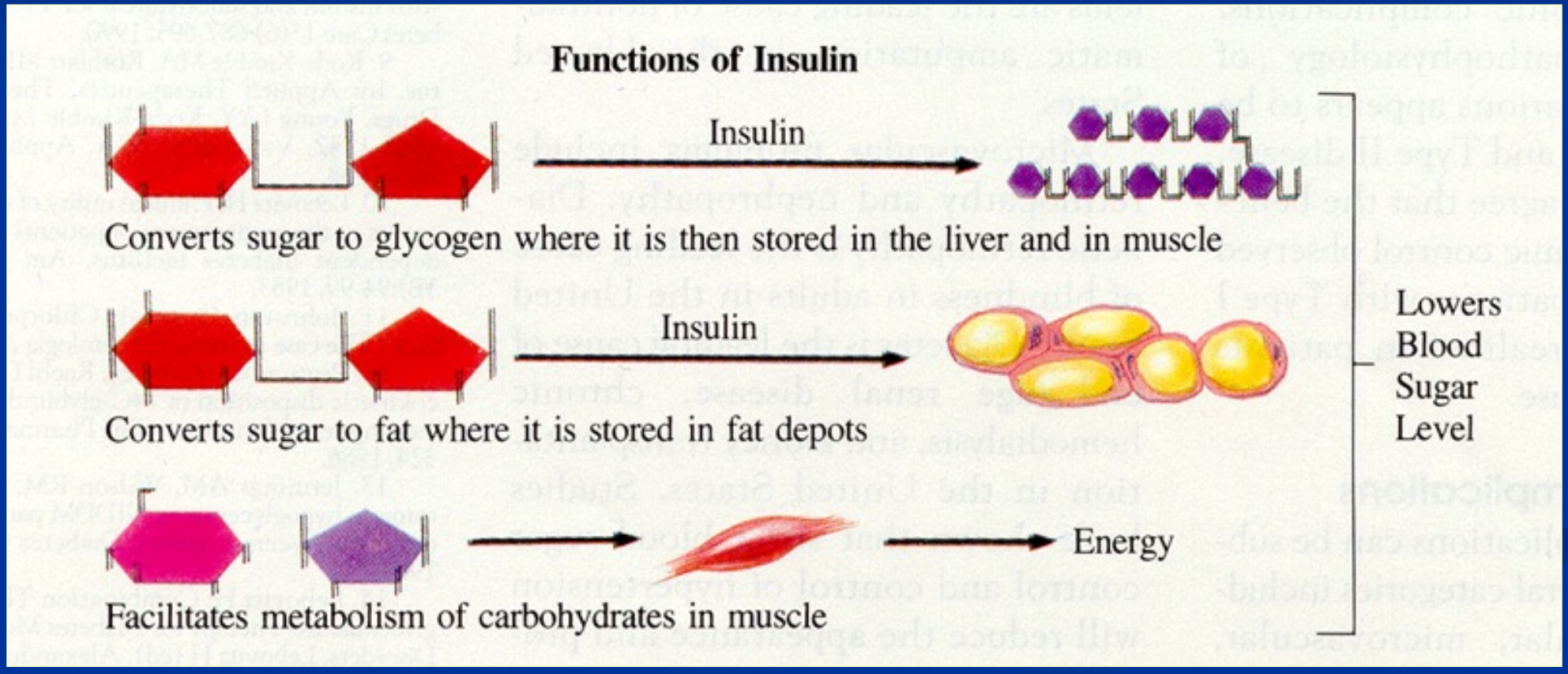
TRANSPORT (ENTRY) SYSTEM SPECIFIC
FOR CERTAIN SUGARS:
INSULIN HAS NO EFFECT ON RATE OF UPTAKE



FAT CELLS; MUSCLE CELLS

SPECIFIC TRANSPORT SYSTEM KEPT
INHIBITED OR COVERED:
INSULIN REMOVES COVER AND THUS
PROMOTES UPTAKE

Function of Insulin



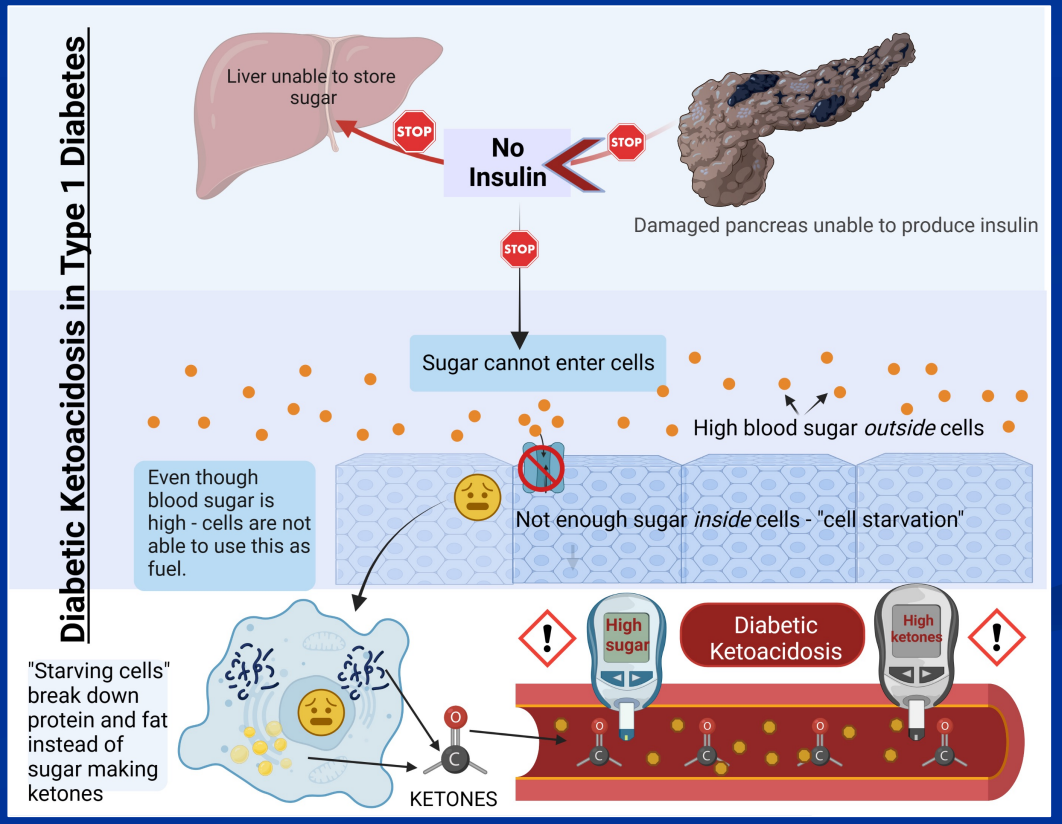
I. General Considerations

A. Type I ("Juvenile Onset" or IDDM)

- Type I diabetes represents 5-10% of adult diabetics

- Type I DM is characterized by autoimmune destruction of pancreatic beta cells → inability to produce and secrete insulin → IDDM

- Type I diabetics are subject to diabetic ketoacidosis (DKA)

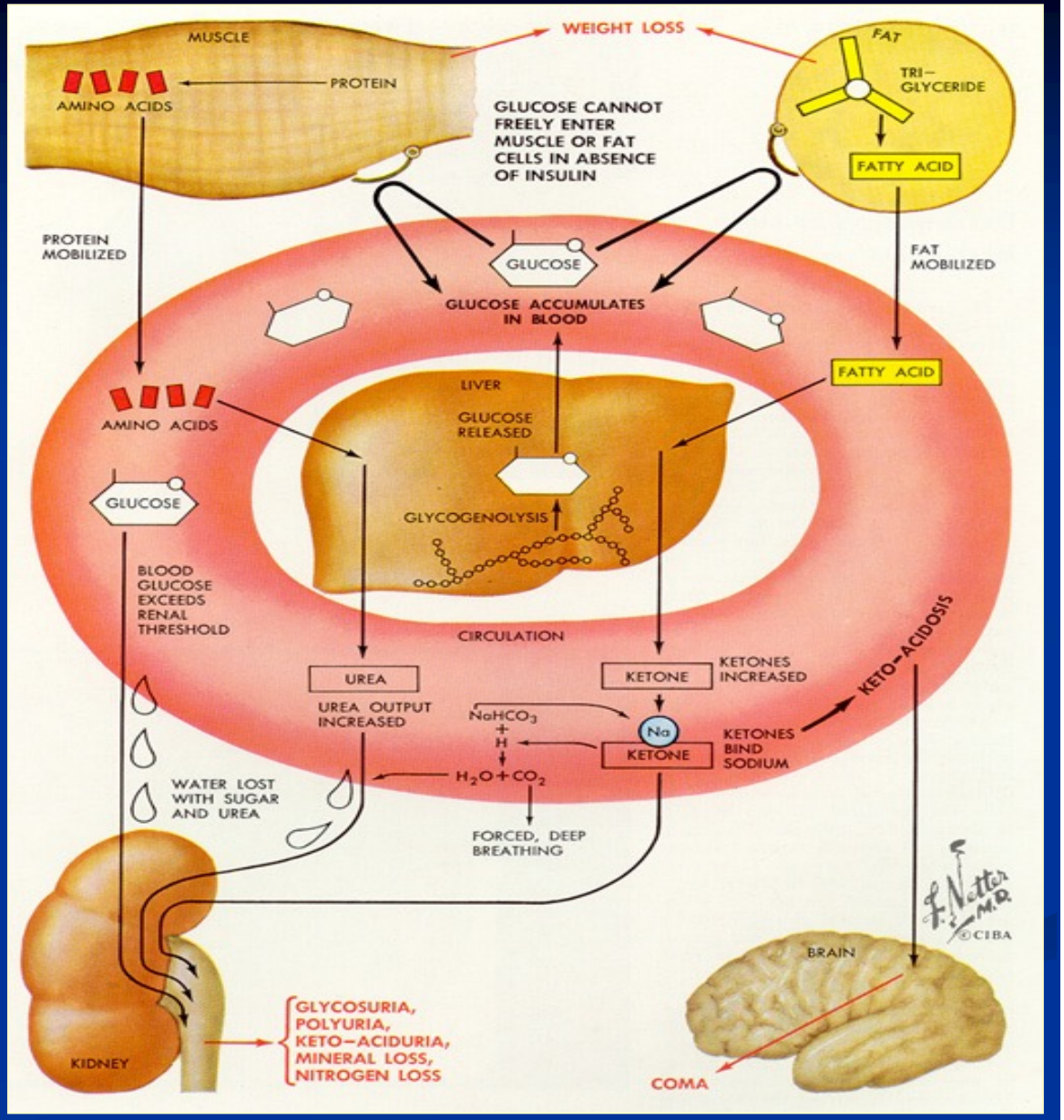


I. General Considerations

A. Type I DM

Diabetic Ketoacidosis (DKA)

- Fatty acids are converted to glucose by the liver, releasing ketones into the bloodstream → DKA
- DKA is a life-threatening medical emergency.

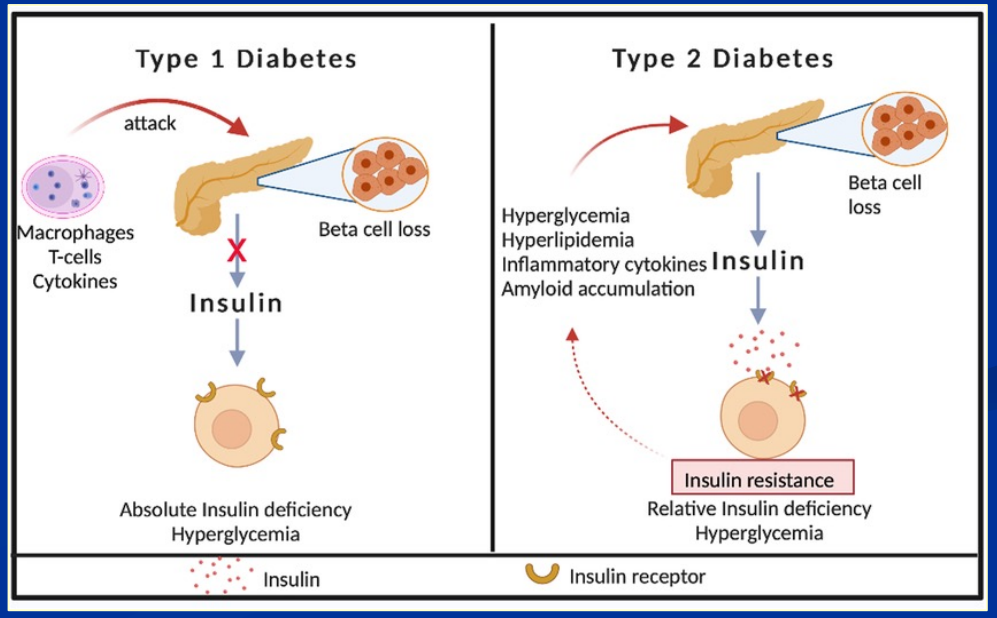


Normal Values
BG: 90-110 mg/dL
pH: 7.35-7.45
Bicarbonate: 21-28 mEq/L

I. General Considerations

B. Type II ("Adult Onset" or NIDDM)

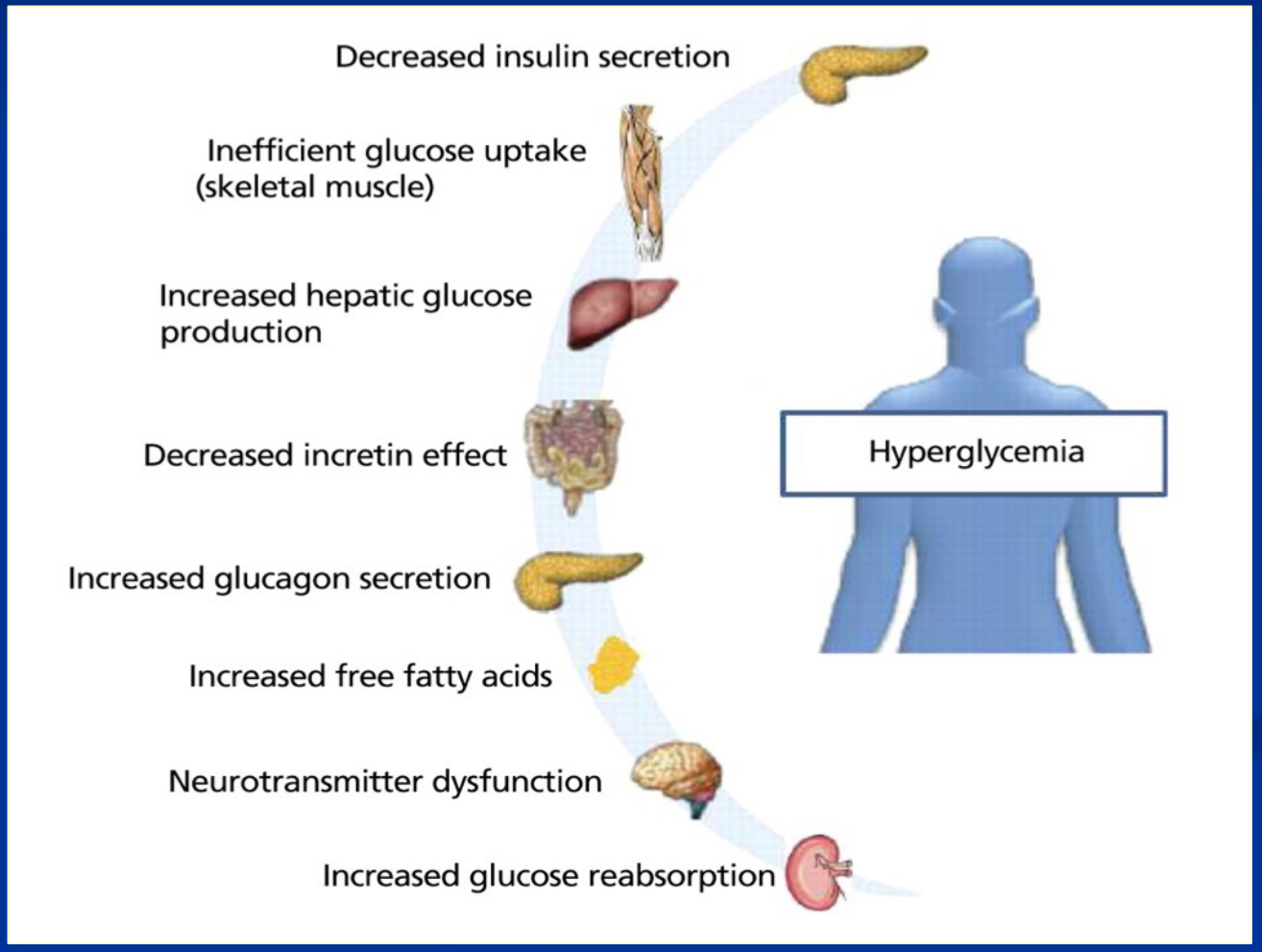
- Type II DM is characterized by a progressive deficiency of insulin secretion and insulin resistance → hyperglycemia.
- Type II diabetics are subject to hyperosmolar hyperglycemic state (HHS) → severe dehydration and obtundation.
- In Type II DM, there is sufficient insulin production to prevent DKA.
- Although DKA is uncommon in Type II DM, it is more likely to occur during acute illnesses (e.g., sepsis, acute MI).



I. General Considerations

B. Type II Diabetes Mellitus (cont.)

- Type II DM is a complex disease involving many pathologic factors …



II. Acute Complications of Diabetes

- Acute Symptoms: polydipsia, polyuria, polyphagia, nocturia, hypoglycemia, fatigue, and blurred vision.
- Type I DM: Diabetic Ketoacidosis (DKA) → Coma
- Type II DM: Hyperosmolar Hyperglycemic State (HHS) → Non-Ketotic Coma

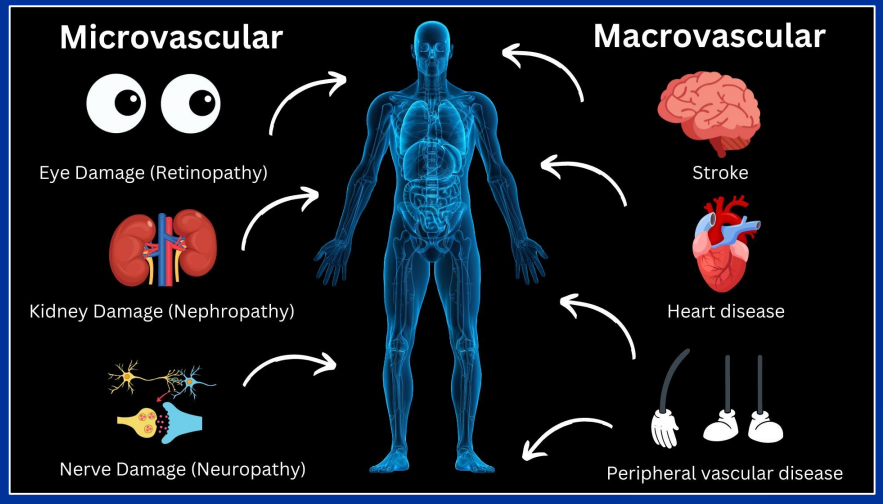
Diagnostic Criteria for Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS)

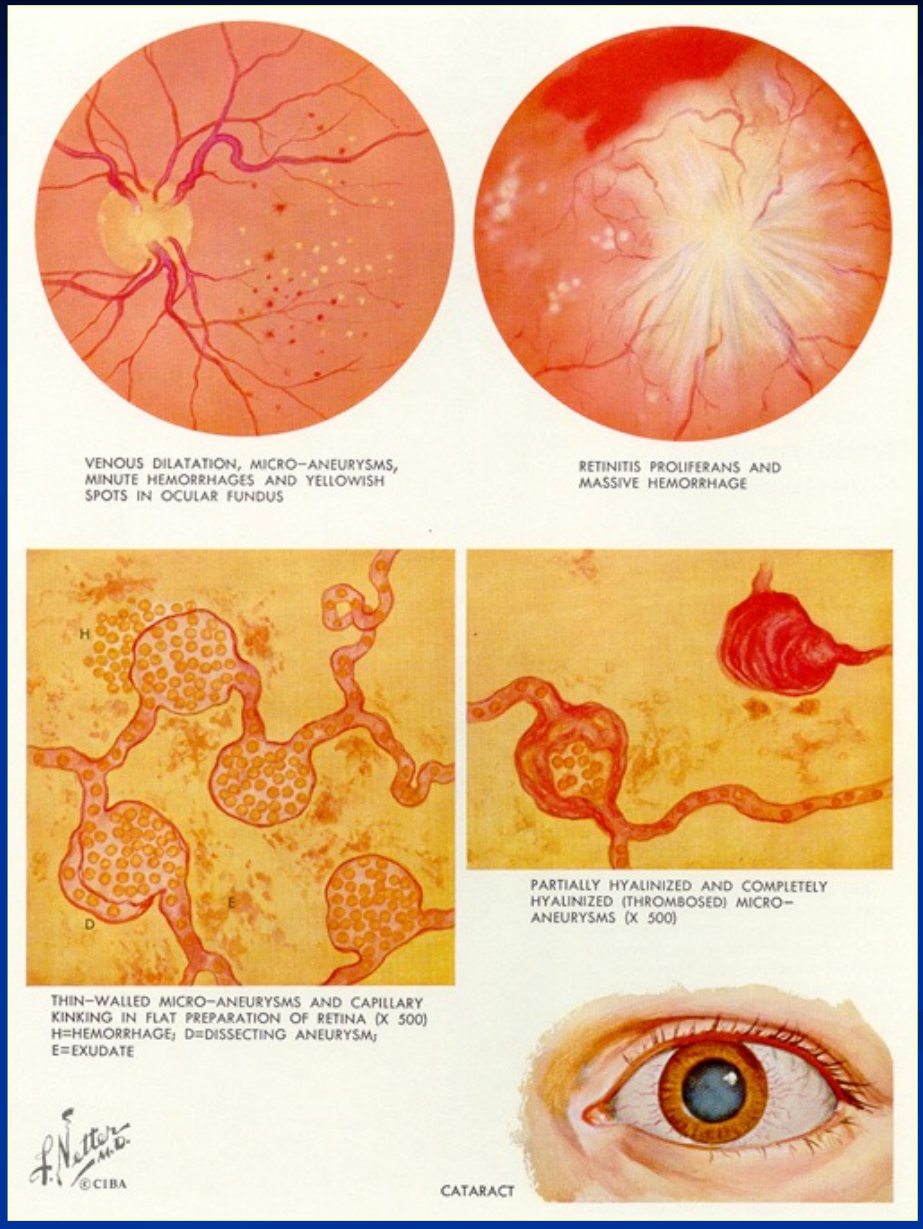
	Diabetic ketoacidosis			*Hyperosmolar hyperglycemic state*
Criterion	*Mild (serum glucose > 250 mg per dL [13.88 mmol per L])*	*Moderate (serum glucose > 250 mg per dL)*	*Severe (serum glucose > 250 mg per dL)*	*Serum glucose > 600 mg per dL (33.30 mmol per L)*
Anion gap*	> 10 mEq per L (10 mmol per L)	> 12 mEq per L (12 mmol per L)	> 12 mEq per L (12 mmol per L)	Variable
Arterial pH	7.24 to 7.30	7.00 to < 7.24	< 7.00	> 7.30
Effective serum osmolality*	Variable	Variable	Variable	> 320 mOsm per kg (320 mmol per kg)
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma
Serum bicarbonate	15 to 18 mEq per L (15 to 18 mmol per L)	10 to < 15 mEq per L (10 to < 15 mmol per L)	< 10 mEq per L (10 mmol per L)	> 18 mEq per L (18 mmol per L)
Serum ketone†	Positive	Positive	Positive	Small
Urine ketone†	Positive	Positive	Positive	Small

III. Chronic Complications of Diabetes Mellitus

A. Microvascular and Macrovascular Disorders

1. Microvascular Disorders: Retinopathy



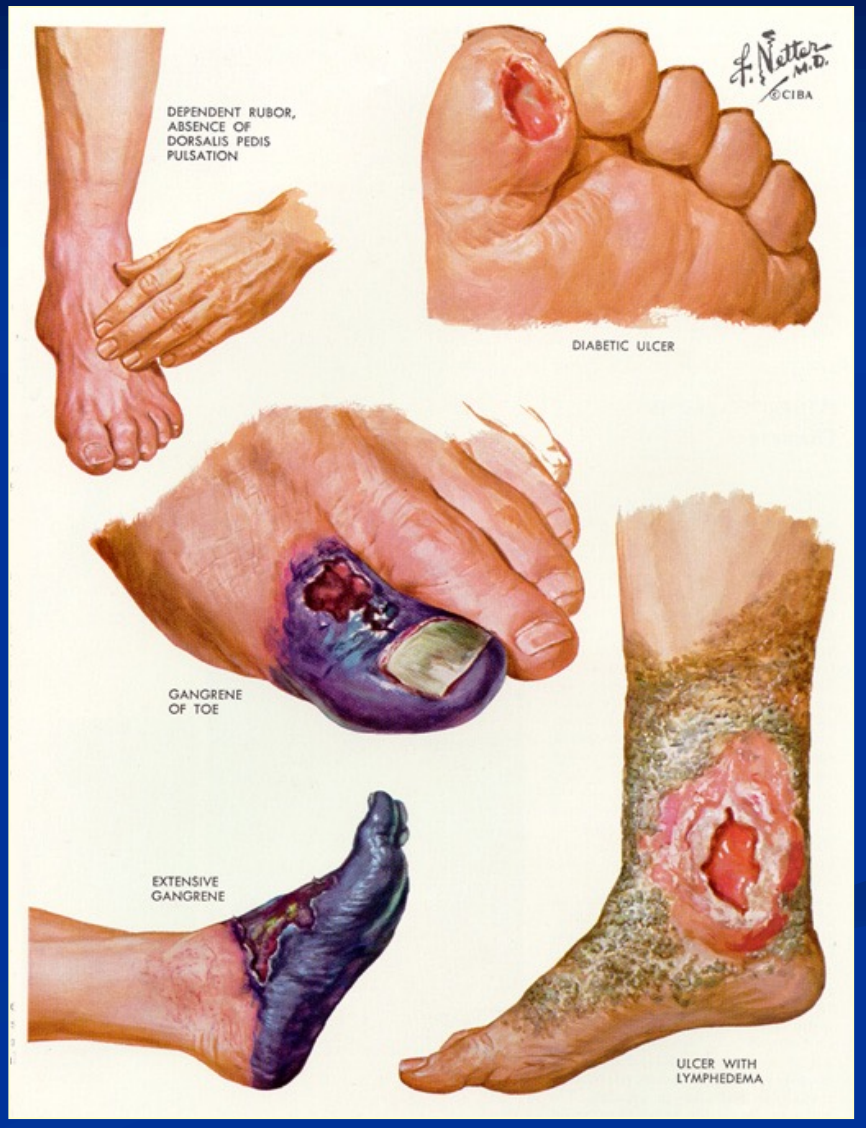


III. Chronic Complications of Diabetes Mellitus (cont.)

A. Microvascular and Macrovascular Disorders

2. Macrovascular Disorders

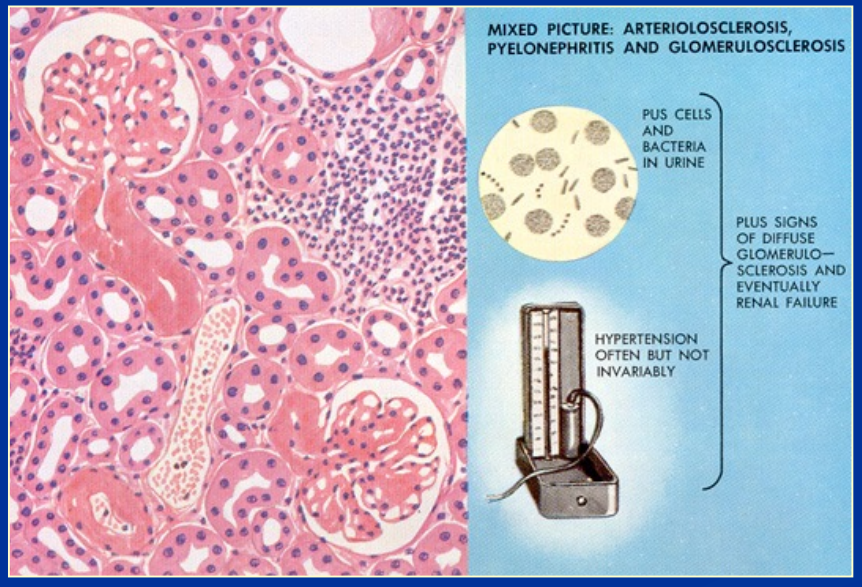
- Cerebrovascular Disease
  → CVA (Stroke)
- Cardiovascular Disease
  → CAD (coronary artery disease) → MI
- Peripheral Vascular Disease
  → Diabetic Foot Infections
  → Gangrenous Extremities
  → Limb Amputations

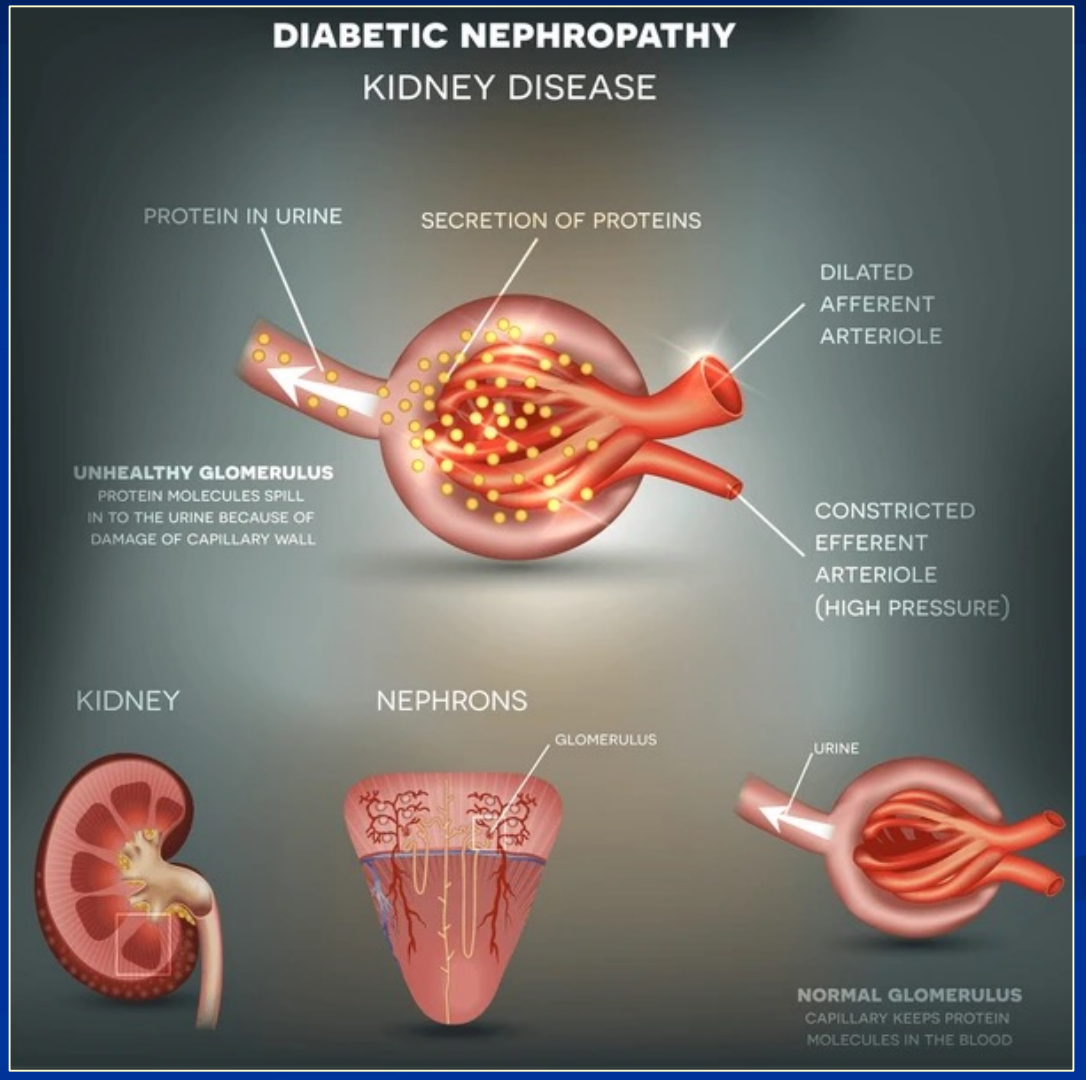


III. Chronic Complications of Diabetes Mellitus (cont.)

B. Kidney Disorders

1. Chronic Kidney Disease (CKD, DKD)
2. Pyelonephritis

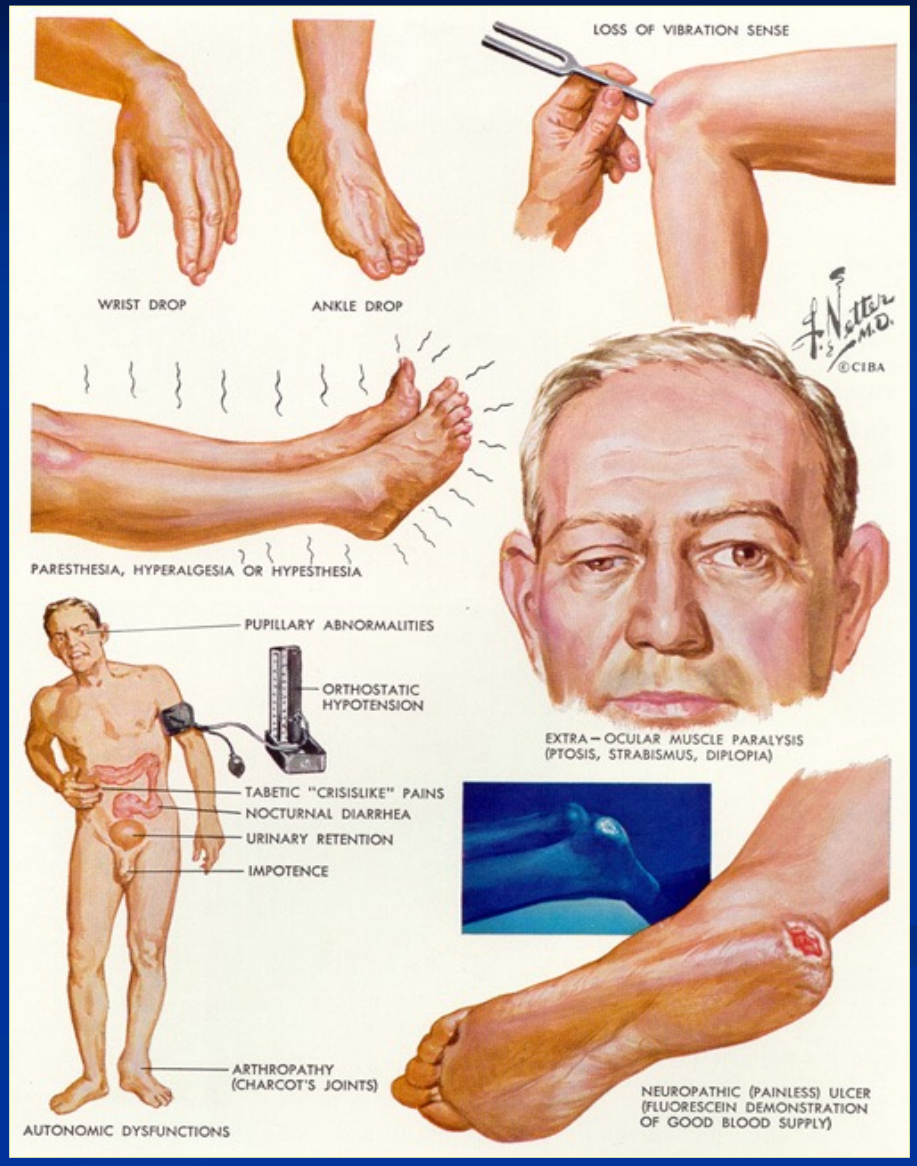




III. Chronic Complications of Diabetes Mellitus (cont.)

C. Diabetic Neuropathy

1. Chronic Neuropathic Pain
2. Paresthesia
3. Orthostatic Hypotension
4. Gastroparesis
5. Diabetic Foot Ulcers



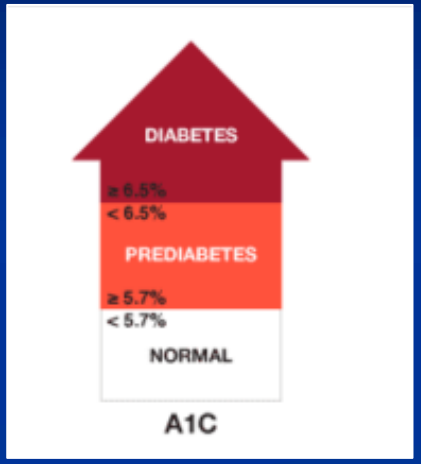
IV. Criteria for Diagnosis of PRE-DIABETES & DIABETES

Criteria for the Diagnosis of PREDIABETES
A1C ≥5.7%, but <6.5% **OR** Fasting plasma glucose ≥100 mg/dL (fasting is no food for at least 8 hours), but <126 mg/dL **OR** Two-hour plasma glucose ≥140 mg/dL during an oral glucose tolerance test, but <200 mg/dL
Criteria for the Diagnosis of DIABETES
A1C ≥6.5% **OR** Fasting plasma glucose ≥126 mg/dL (fasting is no food for at least 8 hours) **OR** Two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test **OR** Symptomatic patients with a random plasma glucose ≥200 mg/dL

IV. Criteria for Diagnosis of Pre-Diabetes and Diabetes (cont.)

- A1C may also be reported as "Estimated Average Glucose (eAG)"

A1C	eAG	
%	mg/dL	mmol/L
6	126	7.0
6.5	140	7.8
7	154	8.6
7.5	169	9.4
8	183	10.1
8.5	197	10.9
9	212	11.8
9.5	226	12.6
10	240	13.4



V. Treatment: Lifestyle Modifications

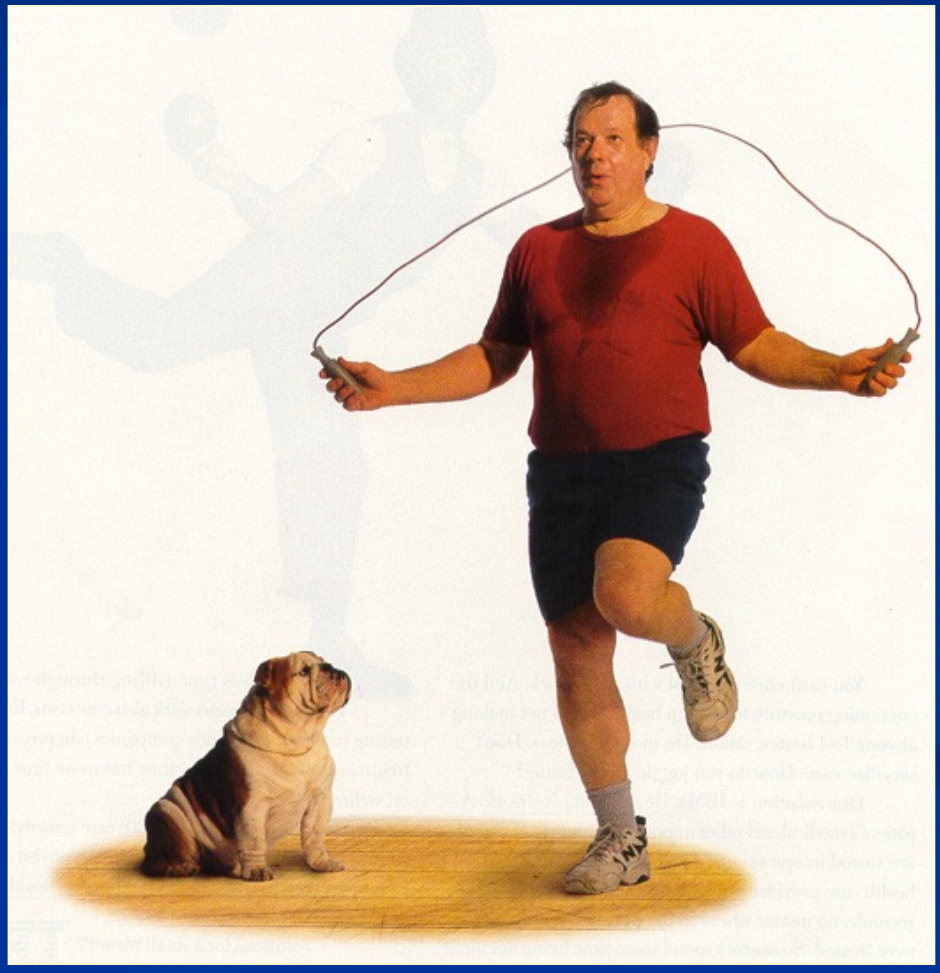
A. Nutrition

B. Timing of Meals

C. Body Weight Considerations

D. Exercise

1. Exercise improves utilization of glucose.
2. Exercise improves insulin utilization.
3. Exercise improves lipid profile.



V. Treatment: Lifestyle Modifications

E. BEE (basal energy expenditure) formula allows us to estimate daily caloric requirements.

Sample Caloric Requirement (BEE) Calculation for Stressed Patients

Female: 655 + (9.6 x wt. in kg) + (1.85 x ht. in cm) – (4.7 x age)

Male: 66 + (13.7 x wt. in kg) + (5.00 x ht. in cm) – (6.8 x age)

Sample Calculation (based on patient-specific parameters: ht, wt, age, and disease state)

S.Y. is a 64 year-old female patient with major sepsis. Calculate her caloric requirement based on her pathologic condition. Her height is 5'4" and body weight is 140 pounds.

Conversion Factors:

- body weight from pounds to kg. : 140 lbs / 2.2 = 63.64 kg
- height from inches to cm. : 5'4" = 64 inches x 2.54 = 162.56 cm

BEE = 655 + (9.6 x **63.64**) + (1.85 x **162.56**) – (4.7 x **64**)

= (655 + 610.94 + 300.74) – (300.8)

= 1265.88 kcal / day

Multiply the BEE value by the appropriate "disease stress factor", which provides additional calories to account for the degree of physiologic stress (based on increased metabolic requirement during pathologic condition – i.e., major sepsis).

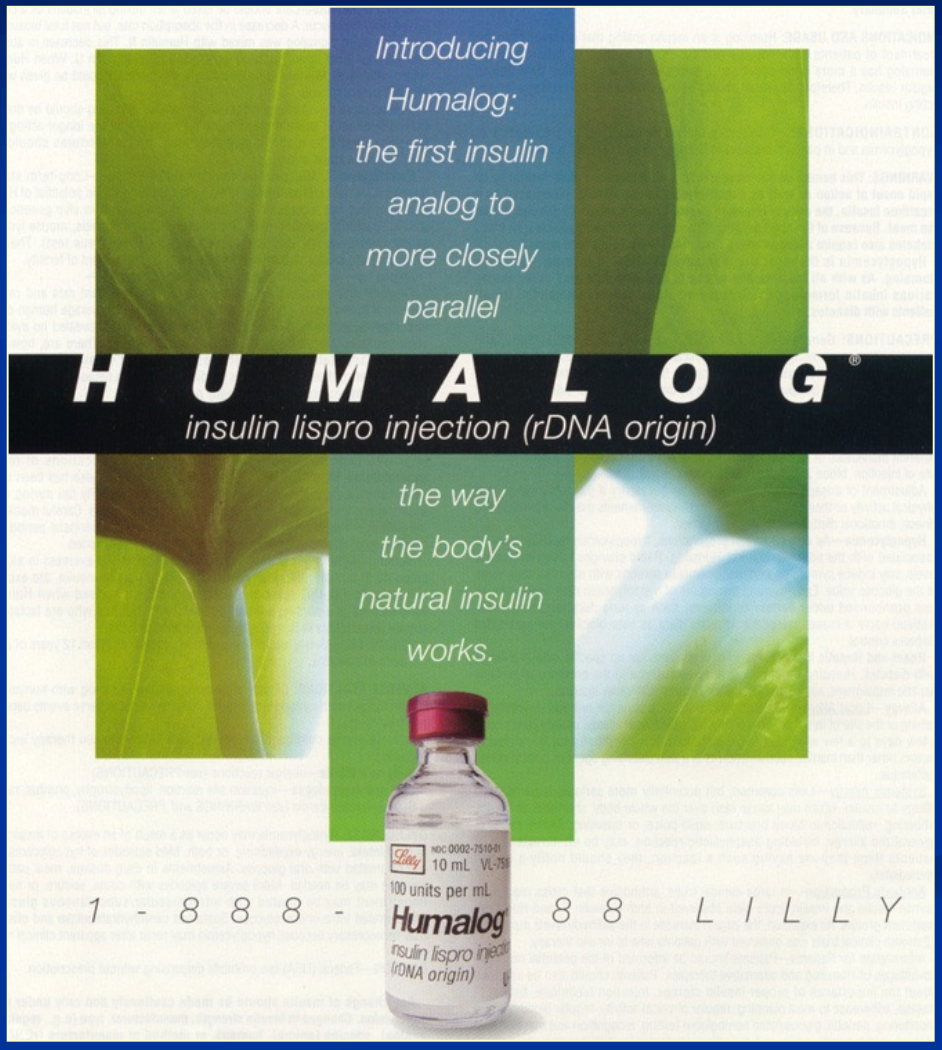
BEE for major sepsis = 1.5 x 1265.88

Answer → 1898.82 kcal / day

VI. Pharmacologic Management of IDDM

A. Insulin Products

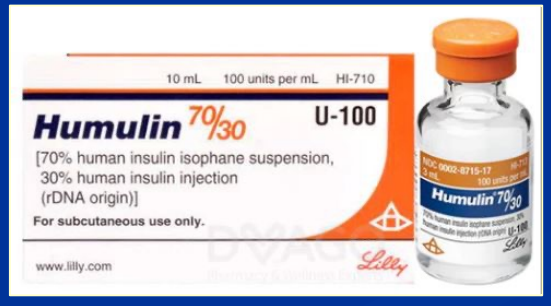
1. Rapid-Acting Insulin: Humalog (Lispro)
   - onset: 10 - 15 min
   - peak: 45 min - 1 hour
   - duration: 2 - 4 hours



VI. Pharmacologic Management of IDDM (cont.)

A. Insulin Products (cont.)

2. Short-Acting Insulin: Regular Insulin (Humulin R)
   - onset: 30 - 60 min → peak: 2 - 4 hours
   - duration: 4 - 8 hours
3. Intermediate-Acting Insulin: NPH (Humulin N)
   - onset: 2 – 4 hours → peak: 4 – 10 hours
   - duration: 10 – 18 hours



VI. Pharmacologic Management of IDDM (cont.)

A. Insulin Products (cont.)

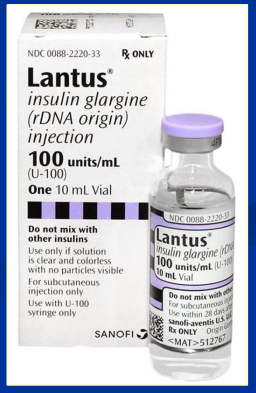
3. Long-Acting Insulin:

   a. Detemir (Levemir) → BID

      - onset: 2 – 3 hours
      - peak: 6 – 8 hours
      - Duration: 5.7 – 23.2 hours

   b. Glargine (Lantus) → Q24H (mostly) / BID

      - onset: 4 - 6 hours →
      - peak / duration: same
        action throughout the day for 24 hours

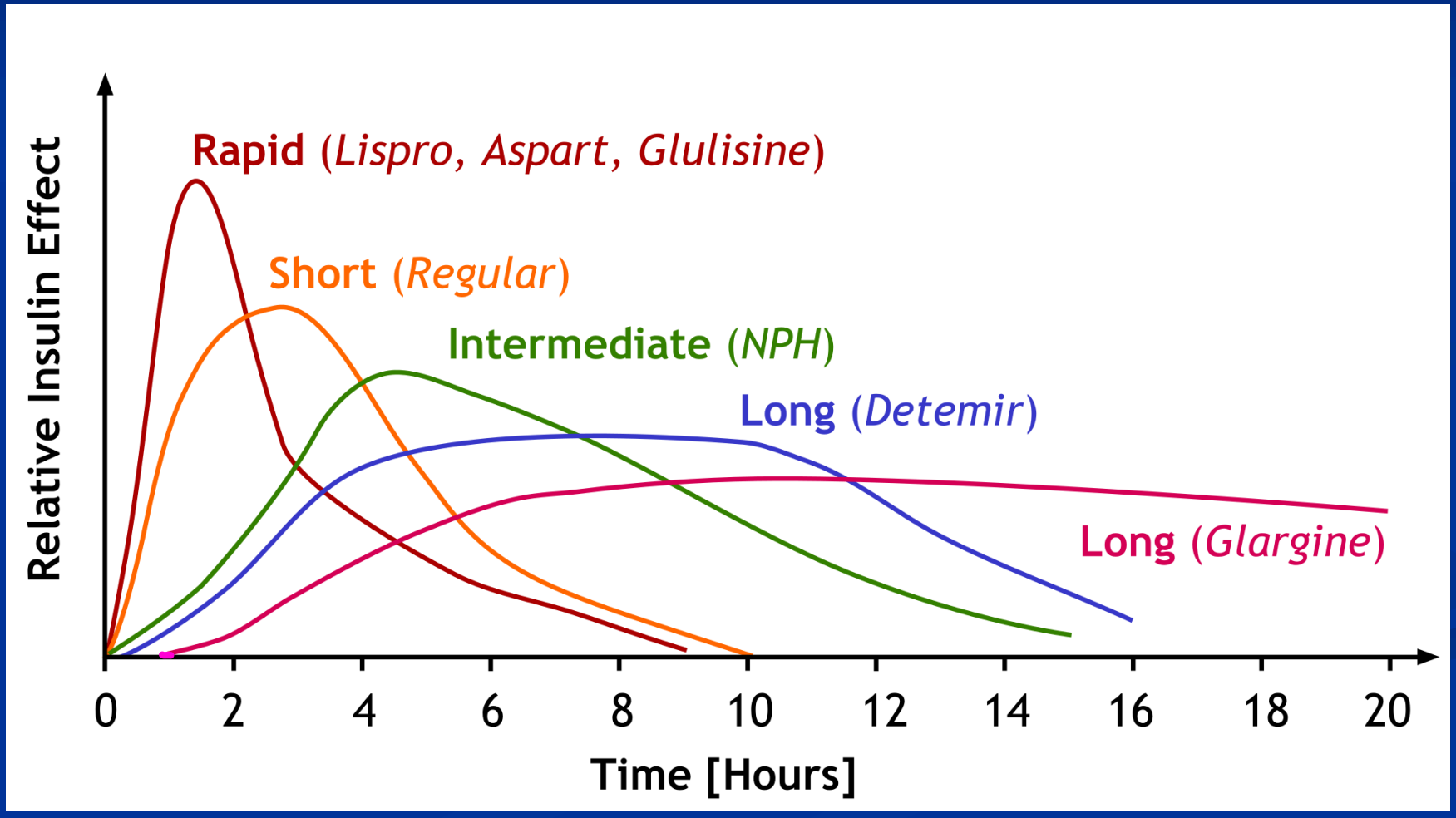


Insulin Comparison Chart

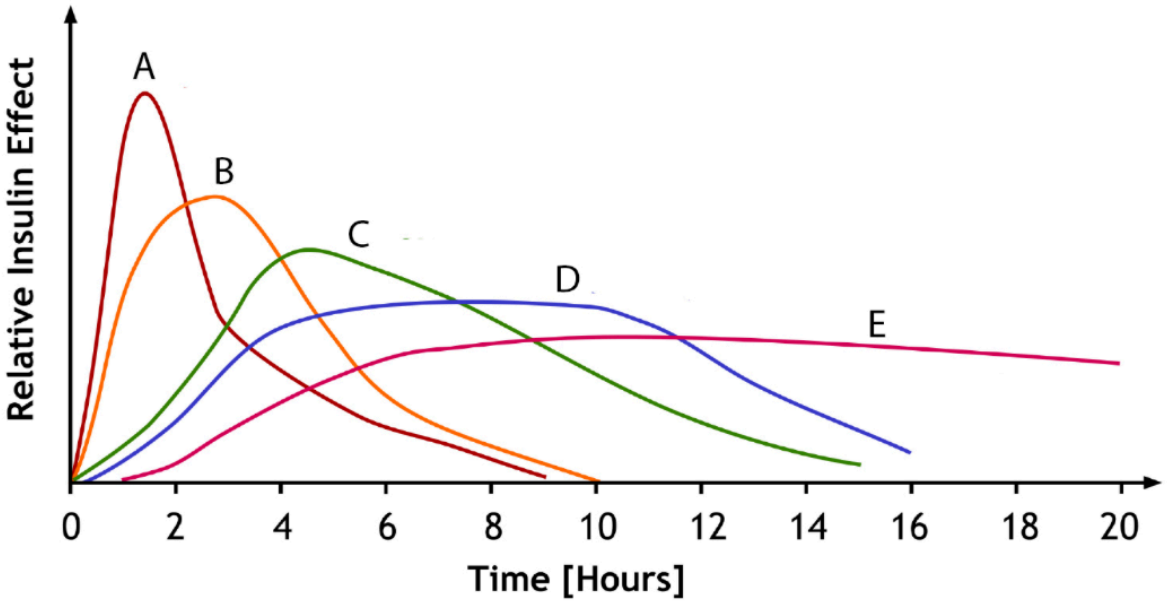
Insulin Name	When does it start working? (onset)	When will the effect be the greatest? (peak)	How long will it lower blood glucose? (duration)	Notes for Use	Cost estimate
Rapid Acting					
Lispro (Humalog™)	<15 minutes	0.5-3 hours*	3-5 hours	If mixing with NPH, rapid acting insulin should be drawn into syringe first. Mixture should be given immediately to avoid effects on peak action.	$96 (10 ml vial) $183 (5x3 ml pen cartridges)
Aspart (Novolog™)	<15 minutes	0.5-3 hours*	3-5 hours		$102 (10 ml vial) $205 (5x3 ml pen cartridges)
Glulisine (Apidra™)	<15 minutes	0.5-3 hour*	3-5 hours		$96 (10 ml vial) $184 (5x3 ml pen cartridges
Short Acting					
Regular (Novolin R™ or Humulin R™)	0.5-1 hour	2-4 hours	4-8 hours	May be mixed with NPH in same syringe. Mixing order should be the clear regular drawn up first, then the cloudy NPH (ie "clear to cloudy").	$53 (10 ml vial Humulin or Novolin) $121 (5x3 ml Novolin pen cartridges) $89 (5x3 ml Innolet cartridges)
Intermediate Acting					
NPH (Novolin N™ or Humulin N™)	2-4 hours	4-10 hours	10-18 hours	Available as pen or in vial to be used with syringe.	$52 (10 ml vial Humulin or Novolin) $121 (5x3 ml pen cartridges) $91 (5x3 ml Innolet cartridges)
Long Acting					
Glargine (Lantus™)	4-6 hours	Same action throughout the day	24 hours	Do not mix with other insulins. Available as pen or in vial. Duration (clinical trial data): 6 hrs (0.1 U/kg), 12 hrs (0.2 U/kg),20 hrs (0.4 U/kg), 23 hrs (0.8 U/kg and 1.6 U/kg)	$97 (10 ml vial) $177 (5x3 ml Solostar pen cartridges)
Detemir (Levemir™)	2-3 hours	6-8 hours	Dose-dependent 5.7-23.2 hours		$95 (10 ml vial) $182 (5x3 ml pen cartridges)
Combinations					
Humulin or Novolin 70/30	0.5-1 hour	2-10 hours	10-18 hours	70% NPH +30% regular insulin. Insulin action includes 2 peaks (1 from each formulation).	$54 (10 ml vial) $135 (5x3 ml pen cartridges) $94 (5x3 ml Innolet cartridges)
Novolog Mix 70/30 Humalog Mix 75/25 or 50/50	<15 minutes	1-2 hours	10-18 hours	Novolog Mix: aspart protamine 70% + aspart 30% Humalog mix: 75/25=75% lispro protamine + 25% lispro 50/50=50% lispro protamine + 50% lispro Insulin action includes 2 peaks (1 from each formulation).	Humalog Mix 75/25: $102 (10 ml vial), $174 (5x3 ml pen cartridges)

Time Profile Curves of Current Insulin Products

Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra), Regular (Humulin R), NPH (Humulin N), Detemir (Levemir), and Glargine (Lantus)



Match each insulin product with its corresponding time profile curve (A → E).



1. Lantus (Glargine) .....
2. Humulin R (Regular) .....
3. Levemir (Detemir) .....
4. Humalog (Lispro) .....
5. Humulin N (NPH) .....

A. Curve B (Short-Acting)

B. Curve E (Long-Acting → Once Daily Dosing)

C. Curve C (Intermediate-Acting)

D. Curve A (Rapid-Acting)

E. Curve D (Long-Acting → Twice Daily Dosing)

VI. Pharmacologic Management of IDDM (cont.)

B. Insulin Regimens

- General Estimate of Daily Insulin Requirement:
  0.5 - 1.0 units insulin / kg body weight / day
- General Rule: 1 - 2 units insulin → ↓ 30-50 mg/dl BG

- Humalog Sliding Scale Regimen:
  QID (AC & HS)

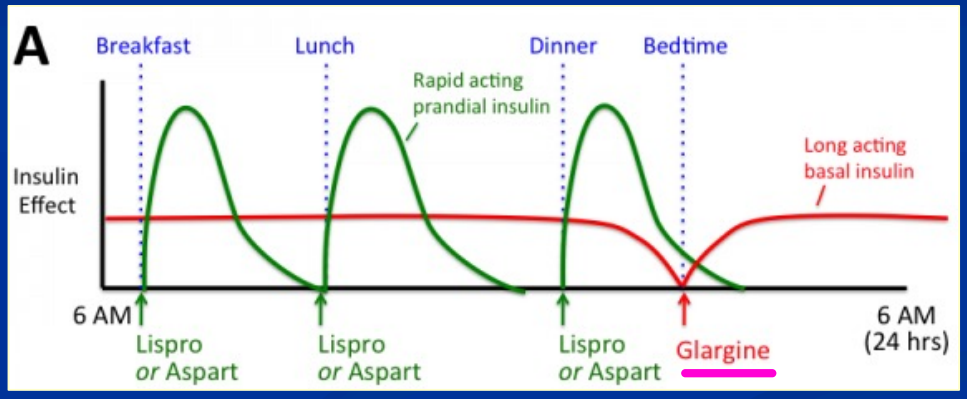
Glucose Level (mg/dL)	Low Dose Regimen (0-6 UNITS) AC & HS	Medium Dose Regimen (0-12 UNITS) AC & HS	High Dose Regimen (0-18 UNITS) AC & HS
< 70	25-50 ml Dextrose 50% IVP		
60 – 150	0	0	0
151 - 199	1	2	4
200 - 249	2	4	6
250 – 299	3	6	8
300 – 349	4	8	12
350 – 399	5	10	14
> 400	6 Call MD/PA	12 Call MD/PA	18 Call MD/PA

B. Insulin Regimens (cont.)

- Method A: Lispro (Humalog) + Glargine (Lantus)
- Method B: Regular Insulin (Humulin R) or Lispro + NPH (Humulin N)

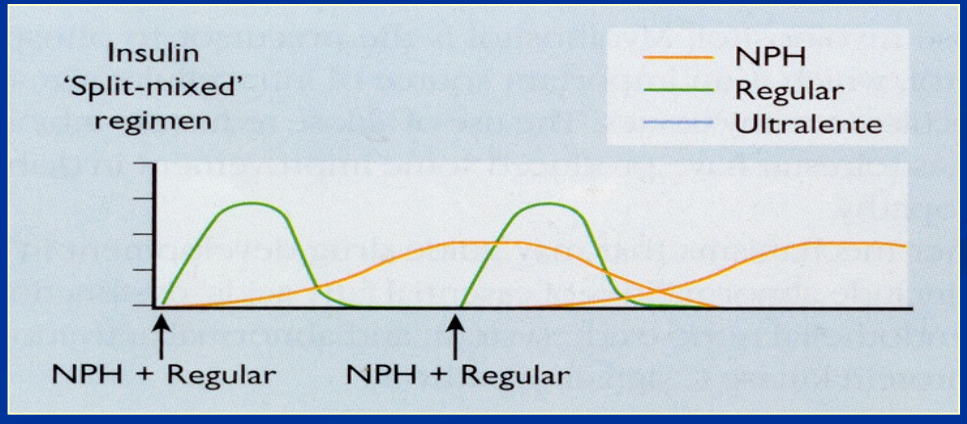
Method A: Basal/Bolus Regimen Mimics Normal Insulin Profile

- Short-Acting Insulin Bolus with Long-Acting Insulin Basal Coverage



Method B: Bolus/Intermediate Insulin Regimen

- 7AM: NPH:Reg (2/3 of daily insulin dose)
- 6 PM: NPH:Reg (1/3 of daily insulin dose)



VI. Pharmacologic Management of IDDM (cont.)

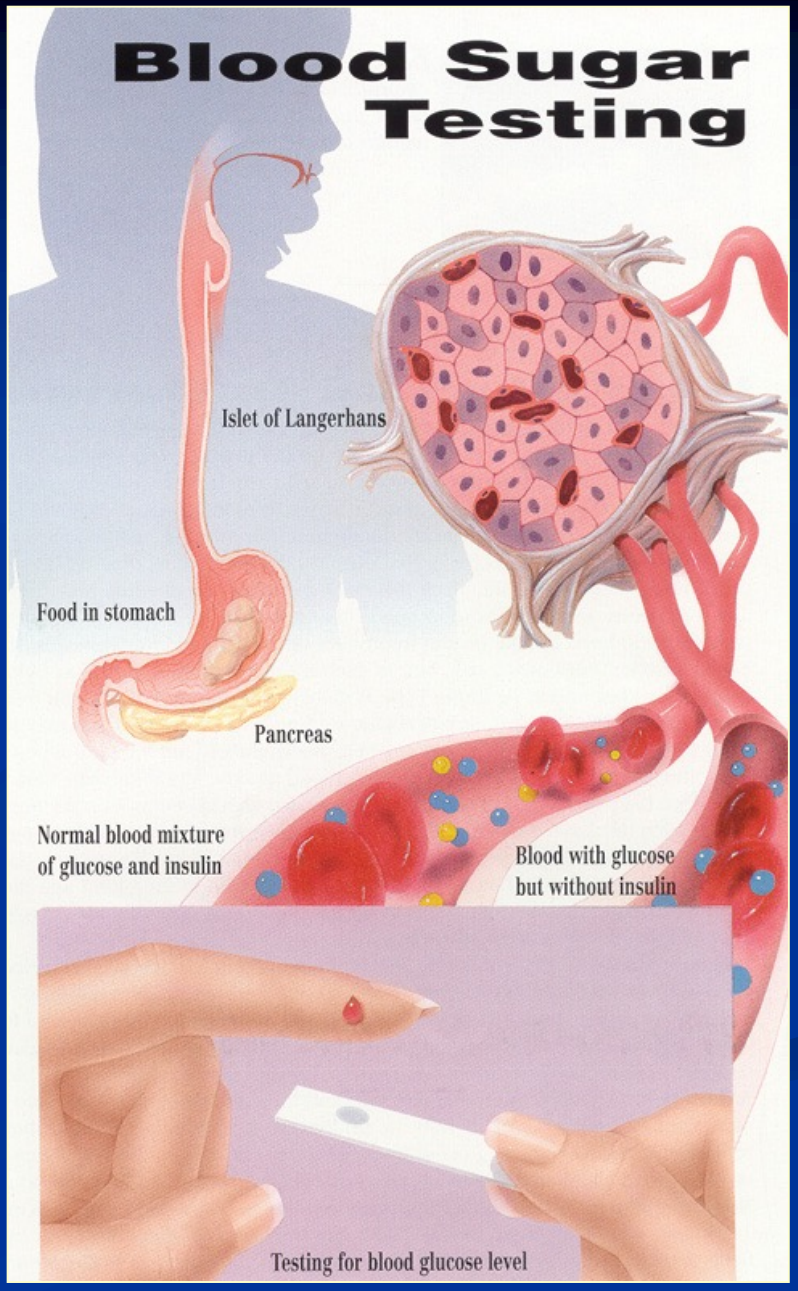
C. Biochemical Indices of Metabolic Control

Index	Normal	Intensive	Acceptable	Poor
Fasting	< 115	70-120	<140	>200
2 hrs pp	< 140	< 180	< 200	> 235
HgbA1c	4 – 6 %	< 6.5 %	< 7 %	> 10%
Urine Gluc	neg	rare	intermit	constant
Urine Keto	neg	rare	rare	intermit

VI. Pharmacologic Management of IDDM (cont.)

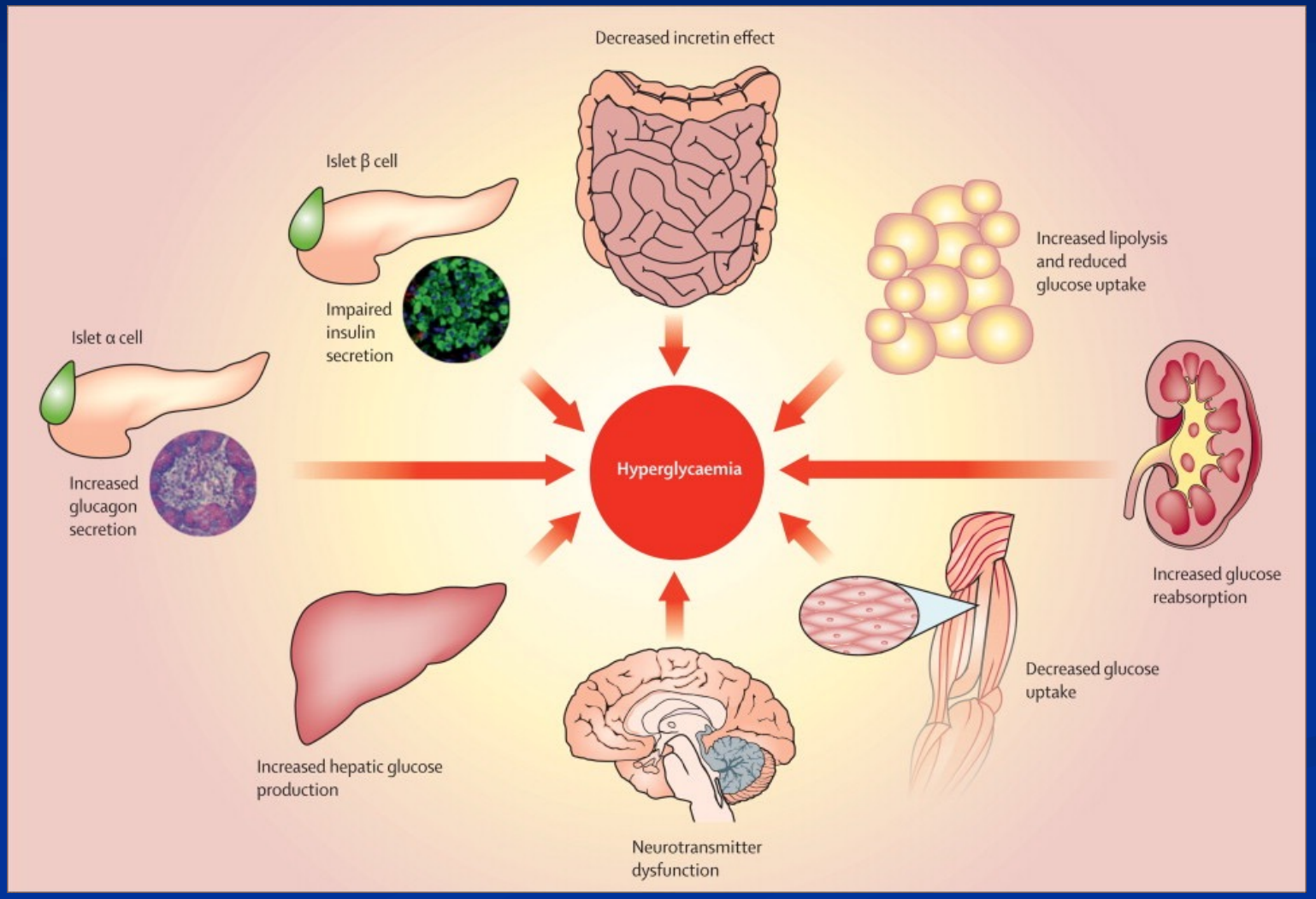
D. Monitoring Patients on Insulin Therapy

- AC & HS
  (before meals and at bedtime)
- occasionally at 0300 during periods of insulin dose adjustments
- whenever hypoglycemia is suspected



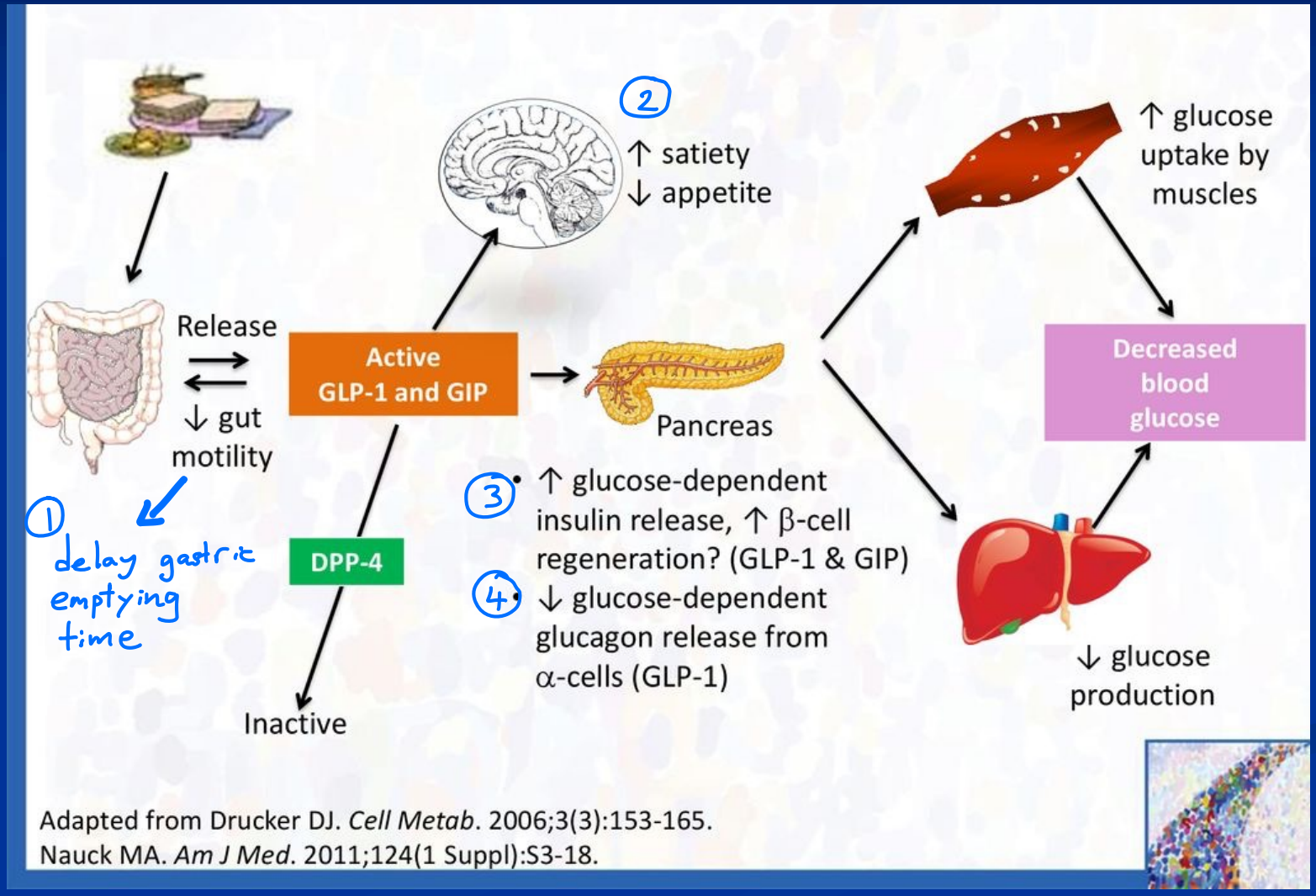
VII. Management of Type II DM

A. Pathogenesis of Type II Diabetes Mellitus



VII. Management of Type II Diabetes Mellitus

A. Pathogenesis of Type II Diabetes Mellitus



VIII. Pharmacologic Management of Type II DM

A. Sulfonylureas

1. MOA: Sulfonylureas increase insulin release by beta cells in the pancreas.

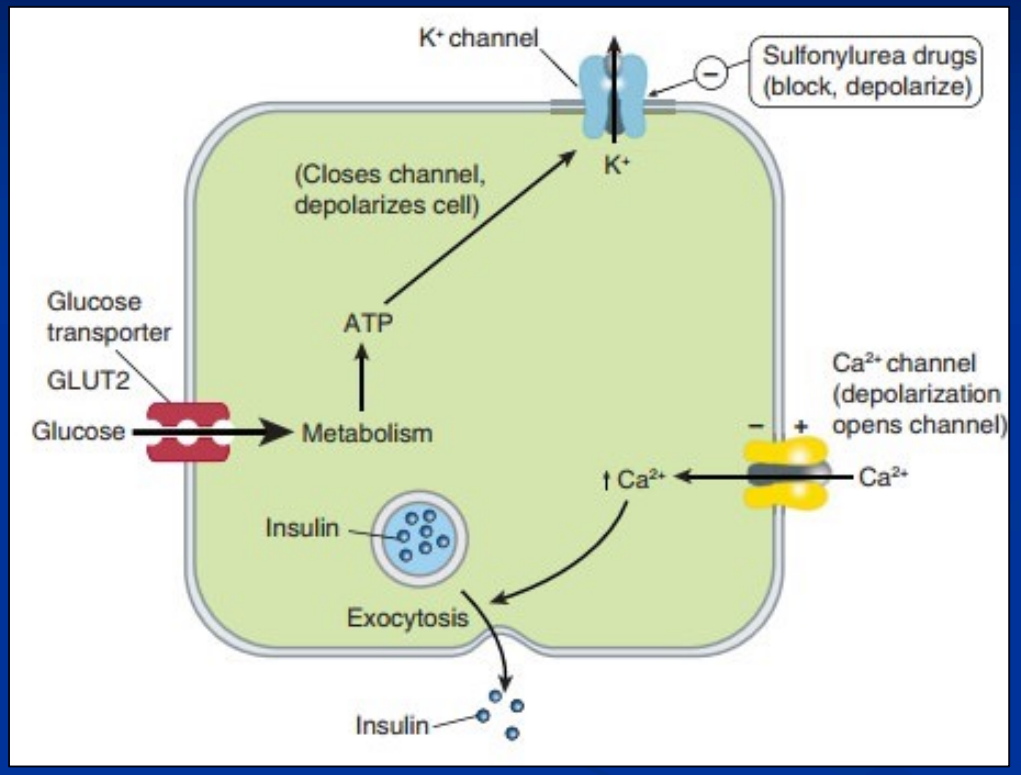
block K channels

↓

depolarizes beta cells

↓

↑ insulin release



In the resting cell with normal (low) ATP levels, potassium diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level. Insulin release is minimal. If glucose concentration rises, AT production increases, potassium channels close, and depolarization of the cell results. As in muscle and nerve, voltage-gated calcium channels open in response to depolarization, allowing more calcium to enter the cell. Increased intracellular calcium results in increased insulin secretion. Insulin secretagogues close the ATP-dependent potassium channel, thereby depolarizing the membrane and causing increased insulin release by the same mechanism.

VIII. Pharmacologic Management of Type II DM

A. Sulfonylureas (cont.)

2. Second Generation Sulfonylureas

- Glipizide (Glucotrol)
- Gyburide (Diabeta, Micronase)
- Glimepiride (Amaryl)

3. Side Effects

- Hypoglycemia
  - most common SE, esp. with glimerpiride
- Weight Gain
  - weight gain may be mitigated with exercise
  - if weight gain worsens rather than improves glycemic control, discontinue sulfonylurea

Sulfonylureas (2nd generation)

	Dose Size / Dose/day (mg)	Peak (hrs)	Dose Interval	Common side effects
Glyburide (Micronase®, DiaBeta®)	2.5, 5mg / 1.25mg – 20mg	4	QD – BID	Weight gain Low Blood Sugar
Glipizide (Glucotrol®)	5, 10mg / 2.5mg – 40mg	1 – 3	QD – BID	Weight gain Low Blood Sugar
Glimepiride (Amaryl®)	1, 2, 4mg / 1 – 8mg	2 – 3	QD	Weight gain Low Blood Sugar

VIII. Pharmacologic Management of Type II DM (cont.)

B. Metformin

1. MOA: decreases hepatic glucose production
2. Other MOAs associated with metformin include …
   - decreases intestinal absorption of glucose
   - improves insulin sensitivity (increases glucose uptake / utilization)
3. Side Effects (GI): diarrhea, nausea, vomiting, bloating, flatulence.
4. Dose: 500 mg – 2500 mg / day in divided doses (BID) with meals.
5. Cautions and Contraindications:

   GFR < 30 ml/min → contraindicated → risk of lactic acidosis
   GFR < 45 ml/min → caution: consider risks vs benefits
6. Metformin is a 1st line agent for newly diagnosed Type II diabetics.

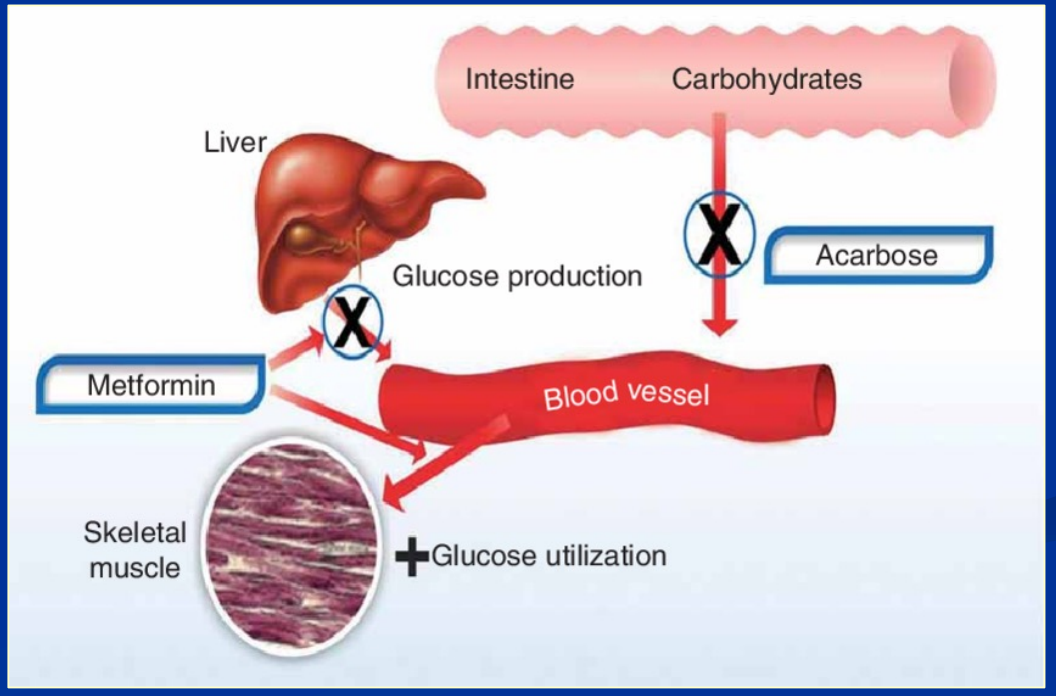
VIII. Pharmacologic Management of Type II DM (cont.)

C. Acarbose (Precose)

1. MOA: inhibits breakdown of carbohydrates by inhibiting alpha glucosidase (secreted by small intestine)

2. Side Effects (GI): abdominal pain, diarrhea, and flatulence (due to undigested carbohydrates in lower GI tract)

3. Dose: 50 – 100 mg TID with first bite of each meal



VIII. Pharmacologic Management of Type II DM (cont.)

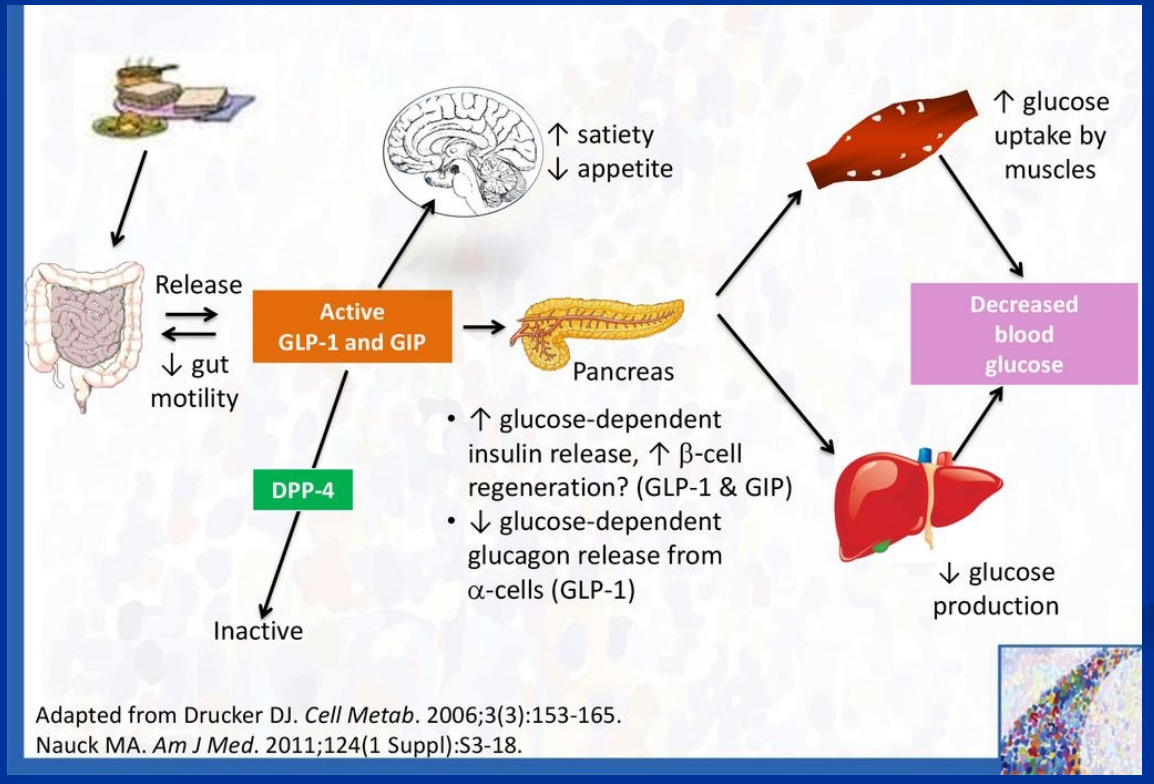
D. Thiazolidinediones (TZDs or Glitazones):
Rosiglitazone (Avandia) and Pioglitazone (Actose)

1. MOA: TZDs increase insulin receptor sensitivity and improve glucose transport in muscle and adipose tissue.
2. Other MOA associated with TZDs includes a decrease hepatic glucose production
3. Side Effects: weight gain, fluid retention, and osteopenia.
4. Pioglitazone (Avandia): 15-30 mg once daily.
5. Cautions and Contraindications:
   - TZDs should not be used in patients with heart failure or any evidence of fluid overload.
   - TZDs should not be used in patients with a history of fracture or at high risk for fracture (e.g., postmenopausal women with low bone mass).

VIII. Pharmacologic Management of Type II DM (cont.)

E. DPP-4 Inhibitors ("Gliptins"):
Sitagliptin (Januvia) and Linagliptin (Tradjenta)

1. MOA: inhibits DPP-4 enzyme → prolongs active incretin levels (GLP-1 and GIP).
2. Side Effects: nasopharyngitis (5%), URI (1%), nausea (2%), diarrhea (4%).
3. Sitagliptin (Januvia): 100 mg PO once daily.



VIII. Pharmacologic Management of Type II DM (cont.)

F. GLP-1 Receptor Agonists

↓

Increase Insulin Release

+

Decrease Glucagon Release

+

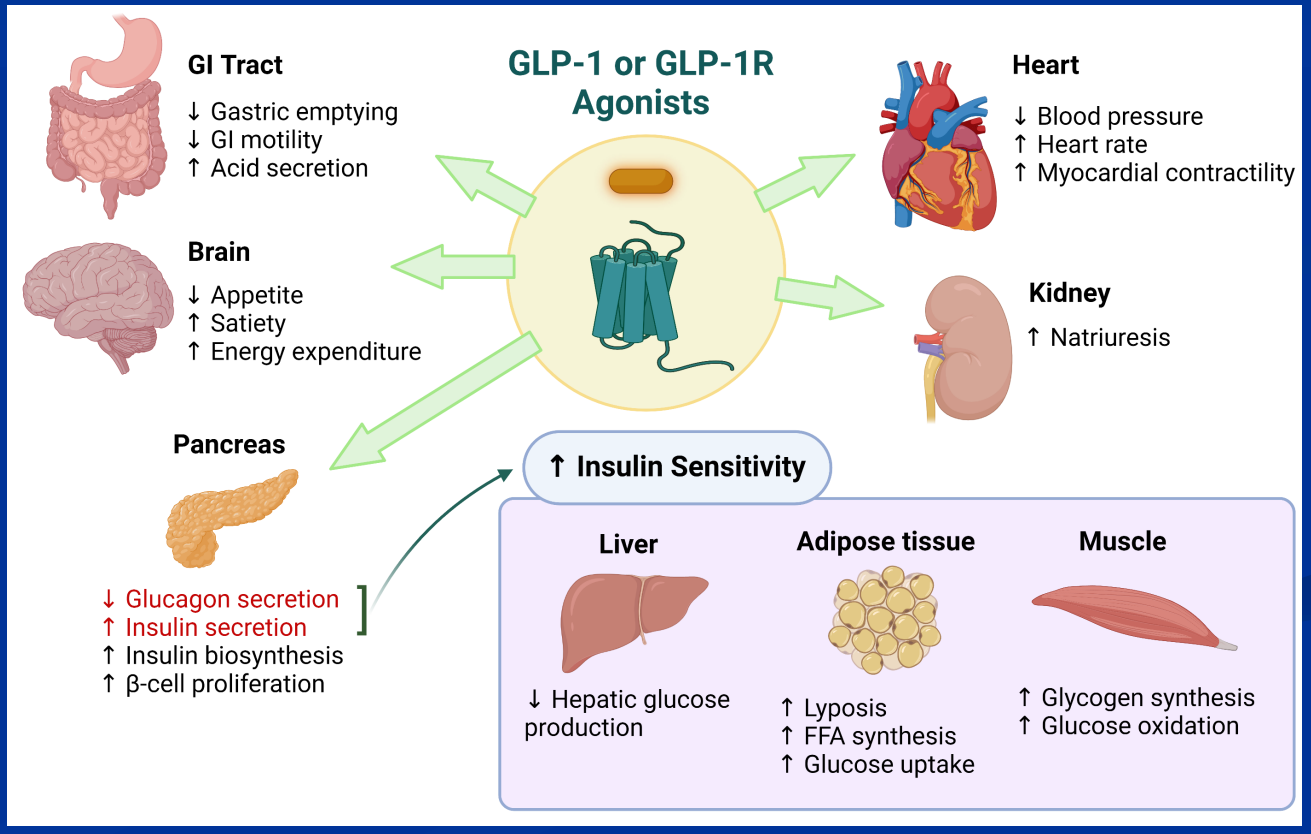
Increase Satiety

+

Delay Gastric Emptying Time

- Adverse Effects (GI): nausea (26-50%), vomiting, and diarrhea.

Semaglutide (Ozempic, Wegovy, Rybelsus): SC/PO
Dulaglutide (Trulicity) SC
Liraglutide (Victoza): SC
Exenatide (Byetta): SC
Tirzepatide (Mounjaro): SC



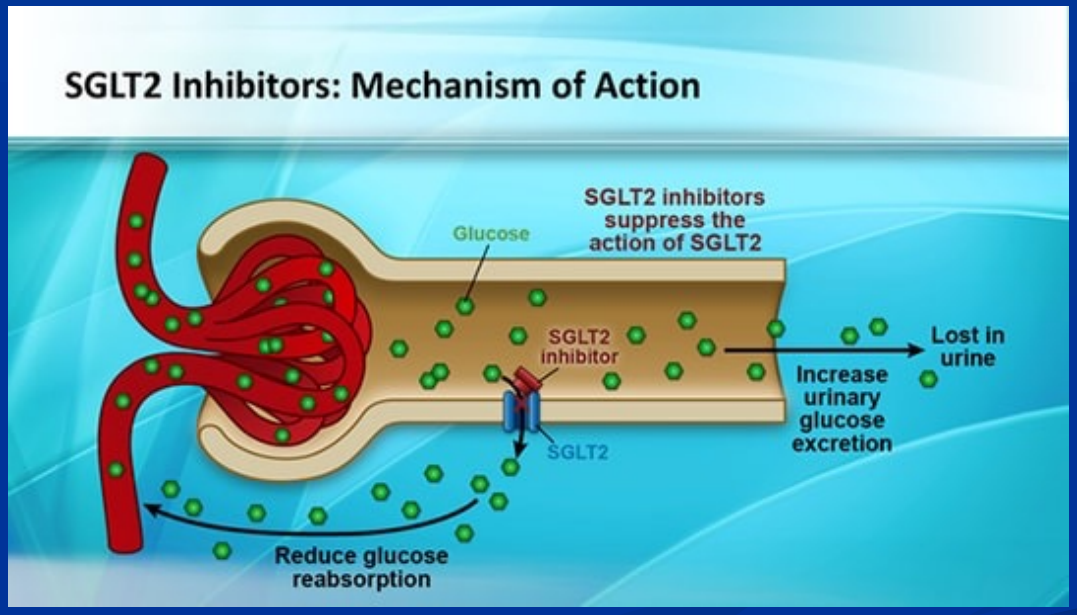
VIII. Pharmacologic Management of Type II DM (cont.)

G. SGLT2 Inhibitors (Sodium-Glucose Transport Inhibitors)

↓

MOA: inhibit SGLT2 transport mechanism → lower blood glucose levels by increasing kidney excretion of glucose into the urine

Canaglifozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)



- Adverse Effects: vaginal candidiasis (10-15%), UTIs (6-8%), dehydration

Summary of Glucose-Lowering Pharmacologic Agents in Type II DM

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Initial therapy			
Lifestyle change to decrease weight and increase activity	1.0 to 2.0	Broad benefits	Insufficient for most within first year owing to inadequate weight loss and weight regain
Metformin	1.0 to 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR <30 mL/min/1.73 m^2)*
Additional therapy¶			
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5 to 3.5	No dose limit, rapidly effective, improved lipid profile	1 to 4 injections daily, monitoring, weight gain, hypoglycemia, analogs are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.5	Weight loss, reduction in major adverse cardiovascular events (liraglutide, semaglutide, dulaglutide) in patients with established CVD and potentially for those at high risk for CVD	Requires injection, frequent GI side effects, expensive
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, DKA
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Possible increased risk of HF with saxagliptin, expensive
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing


PHARMACY
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